NOV 28 1932

VOLUME 50 NUMBER 5

ARCHIVES

OF

INTERNAL MEDICINE

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NOVEMBER, 1932

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 31, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

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Archives of Internal Medicine

VOLUME 50 NOVEMBER, 1932 NUMBER 5

THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN PATIENTS WITH PITUITARY DISEASE

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In the extensive literature on the specific dynamic action of food there have appeared a number of articles relating to the effect of the endocrine glands on this feature of metabolic activity. Experimental studies have led to varied conclusions as to the rôle played by the glands of internal secretion in altering the specific dynamic response to food. Foreign investigators in particular have reported finding this response diminished or completely absent in patients with diseases of the thyroid or pituitary gland.[1] In this country Baumann and Hunt,[2] Foster and Smith[3] and others have noted an abnormal specific dynamic response immediately following the administration of dextrose or amino-acids in rabbits and rats deprived of their thyroid or pituitary glands. Some of the workers, notably Kestner, Liebeschütz-Plaut and Schadow,[4] and Foster and Smith,[3] have reported an increase in the specific dynamic action when preparations of pituitary gland were administered to normal persons, to patients with pituitary disease or to hypophysectomized animals.

An opposing view, however, championed by Lusk,[5] supported by his own work and the observations of Du Bois,[6] Aub and Means,[7] Nord and

From the Surgical Service and the Metabolism Laboratory, Peter Bent Brigham Hospital.

1. Liebesny, P.: Die spezifisch-dynamische Eiweisswirkung, Biochem. Ztschr. **144**:308, 1924. Plaut, R.: Gaswechseluntersuchungen bei Fettsucht und Hypophysiserkrankungen, Deutsches Arch. f. klin. Med. **139**:285 (May 23) 1922. Serejski, M., and Jislin, S.: Endokrine Störungen und spezifisch-dynamische Eiweisswirkung, Ztschr. f. d. ges. exper. Med. **69**:321, 1930.

2. Baumann, E. J., and Hunt, L.: On the Relation of Thyroid Secretion to Specific Dynamic Action, J. Biol. Chem. **64**:709 (July) 1925.

3. Foster, G. L., and Smith, P. E.: Hypophyseal and Replacement Therapy in Relation to Basal Metabolism and Specific Dynamic Action in the Rat, J. A. M. A. **87**:2151 (Dec. 28) 1926.

4. Kestner, O.; Liebeschütz-Plaut, R., and Schadow, H.: Specifisch-dynamische Wirkung, Hypophysenvorderlappen und Fettsucht, Klin. Wchnschr. **5**:1646 (Sept. 3) 1926.

5. Lusk, G.: The Specific Dynamic Action, J. Nutrition **3**:519 (March) 1931.

6. Du Bois, E. F.: Clinical Calorimetry: XIV. Metabolism in Exophthalmic Goitre, Arch. Int. Med. **17**:915 (June) 1916.

7. Aub, J. C., and Means, J. H.: The Basal Metabolism and the Specific Dynamic Action of Protein in Liver Disease, Arch. Int. Med. **28**:173 (Aug.) 1921.

Deuel,[8] Gaebler[9] and Artundo,[10] holds that the endocrine glands have no direct bearing on the specific dynamic action. The present study, though conducted at the beginning in no attempt to take sides in this argument, has supplied evidence in support of Lusk and others so far as pituitary disease in man is concerned. It is published to show that patients with acromegaly or hypopituitarism and those with cerebral tumors either in the region of the pituitary gland or elsewhere have, following a protein-rich meal, a specific dynamic reaction which is well within the range of normal limits.

The first recorded observation on the basal metabolic rate in experimental hypopituitarism in animals (dogs) was made in 1912 by Dr. John Homans of this hospital in collaboration with Dr. Francis Benedict.[11] On the opening of the hospital a year later (1913), a metabolism laboratory was put in operation by Dr. Walter M. Boothby, and it has been customary since that time, as part of the routine examination of patients with pituitary disorders, as often as possible, to record their basal metabolism before and after operation, if operations were performed. It was soon learned that patients with hypopituitary states associated with chromophobe adenomas had a low rate, and that patients with acromegaly had an elevated rate, as recorded in particular by Davidoff and Cushing.[12]

The present observations came to be made in conjunction with the work of Putnam, Benedict and Teel on experimental acromegaly in dogs.[13] As new lots of anterior pituitary lobe extract were being prepared, the laboratory workers were in quest of a test whereby the potency of any given preparation could be established without waiting for the time-consuming growth effect on the experimental animal. The work of Foster and Smith[3] had shown that the specific dynamic action, found wanting in hypophysectomized rats, was present after these animals were given both anterior and posterior lobe extracts. This

8. Nord, F., and Deuel, H. J., Jr.: Animal Calorimetry: XXXVII. The Specific Dynamic Action of Glycine Given Orally and Intravenously to Normal and to Adrenalectomized Dogs, J. Biol. Chem. **80**:115 (Nov.) 1928.

9. Gaebler, H.: Animal Calorimetry: XXXVIII. The Specific Dynamic Action of Meat in Hypophysectomized Dogs, J. Biol. Chem. **81**:41 (Jan.) 1929.

10. Artundo, A.: Action dynamique spécifique chez les chiens hypophysoprives, Compt. rend. Soc. de biol. **106**:139 (Jan. 23) 1931.

11. Benedict, F. G., and Homans, J.: The Metabolism of the Hypophysectomized Dog, J. M. Research **20**:409, 1912.

12. Cushing, H., and Davidoff, L. M.: Studies in Acromegaly: IV. The Basal Metabolism, Arch. Int. Med. **39**:673 (May) 1927.

13. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Studies in Acromegaly: VIII. Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Pituitary Extract, Arch. Surg. **18**:1708 (April) 1929.

suggested to Dr. Teel that if patients with pituitary disease were given the "unknown" anterior lobe extract, there would be an alteration in their metabolic response to a protein meal. This phase of the work did not afford the desired results, but it initiated the present study of the specific dynamic reaction in the group of patients with pituitary disorders. The work at the start was under the supervision of Dr. John Fulton.

MATERIAL

The eighty-two persons studied have been divided into five groups. Fourteen of them had outspoken acromegaly, which in four instances was verified by operation and shown to be associated with a chromophil adenoma. There were seven patients with what has been termed "fugitive" acromegaly.[14] Thirty-two others had the syndrome of pituitary insufficiency and were found to have a chromophobe adenoma. The remaining twenty-nine patients we have divided into (*a*) those with nonadenomatous tumors secondarily affecting the pituitary body and classified as patients with parahypophyseal tumors, and (*b*) those with tumors, or suspected tumors, not in juxtaposition to the gland. The latter group may in some degree serve as controls.

METHODS

This study was in no wise an attempt to determine the total heat effect produced by a fixed meal. A recent very comprehensive account of the specific dynamic action of food in abnormal states of nutrition by Strang and McClugage[15] notes in detail the factors which will determine the accuracy of a study purporting to show the heat effect of food. These authors confess that their "standards of admissibility" are rather exacting. We, however, were interested not so much in observing the precise minor changes in metabolism of a small group of patients as in noting in a larger group the presence or absence of a rise in metabolism after food and the extent of that rise during four hours. Thus, in many instances trial basal metabolism tests were not made preceding the test—a fact which means that the "base line" of the curves of increased metabolism may in some cases be open to question. Since tests were discarded which were grossly out of keeping with previous basal determinations or with the clinical observations on the patient, we do not feel that the figures would be greatly changed had "base line" observations been made to ascertain a constant level of basal metabolism before carrying out the test.[16]

Again, the metabolism was determined for only four hours following the ingestion of the meal. In fact, at the outset readings were made only at one and one-half and two hour intervals until it was appreciated that the peak of the heat rise would frequently be missed in such a short time. These cases are included since they show at least the presence of a heat response to food, though not necessarily the maximum one.

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14. Bailey, P., and Cushing, H.: Studies in Acromegaly: VII. The Microscopic Structure of the Adenomas in Acromegalic Dyspituitarism (Fugitive Acromegaly), Am. J. Path. **4**:545 (Nov.) 1928.

15. Strang, J. M., and McClugage, H. B.: The Specific Dynamic Action of Food in Abnormal States of Nutrition, Am. J. M. Sc. **182**:49 (July) 1931.

16. In this connection one may note that the average total calories per hour in the "unacceptable" cases of Strang and McClugage's series do not differ greatly from the average of the other groups.

The tests were carried out as follows: Fourteen hours after the last meal the basal metabolism was determined indirectly by the Benedict-Roth spirometer with the patient in bed. During this and subsequent determinations his movements were restricted, and he was required to remain perfectly quiet. The basal metabolic rate was taken as the average of two six minute tests which varied from each other by not more than 3 or 4 per cent. The patient was then given 200 Gm. of broiled chopped beef with which he was allowed 100 cc. of water. Determinations were made again at one, two, three and four hours following this meal. Between tests the patient remained quiet in bed but was allowed to read.

METHOD OF TABULATION

The results are shown in tabular form in tables 1 to 5. The metabolism determinations have all been expressed in terms of the percentage variation from normal according to the surface area standards of Aub and Du Bois. This method of tabulation is adopted rather than total calories per hour because it is in common use and appears to us to be the method easily understood. In column 8 of each table are given the basal metabolic rates determined either on the day of the test meal or on days prior to or subsequent to this day. In the next four columns are listed the metabolisms taken at hourly intervals following the ingestion of beefsteak, and expressed in the same manner as the basal rate. The figures in column 13 are a numerical expression of the relation to the basal metabolism of the peak or highest metabolism reached following the test meal. They, therefore, represent the "percentage" increase over the basal "rate," and are derived by dividing the highest increase in metabolism by the basal metabolism. Thus, in patient 1 of table 1, the basal metabolism was 42.3 calories per square meter per hour, which is 107 per cent of normal for a man, aged 28 (39.5 calories), and is therefore expressed as +7. The highest metabolism reached was 53.8 calories per square meter per hour, which is 136 per cent above normal or +36. The increase may be expressed then either as $53.8 - 42.3 = 11.5$ calories or as $36 - 7 = 29$ "points." Reducing this to percentage increase above the basal rate, we get $\frac{11.5}{42.3}$ or $\frac{29}{107}$, or 27.1 per cent. As may be seen from the tables, the peak of the rise in metabolism occurred at various time intervals following the test meal, which is a common finding in the measurement of the specific dynamic action. As noted previously, the tests which ran for only one and one-half or two hours are not a true index of the effects of the meal, but for the purposes of comparison they have been included.

Strang and McClugage[15] have pointed out that there are several technical objections to this method of expressing the fluctuations in metabolism. These points deal with (1) the height of the maximum rate or peak, (2) the numerical value of the basal rate and (3) variations in body surface. In a study of the total heat effect of a meal, one must take account of the extra calories produced throughout the entire time the meal exerts an influence on the metabolism. Thus a sharp rise during any single hour to an abnormally high peak will not serve as an index of the total effect. The true indication must consider the rise at each hour throughout a period of eight hours, or, as Strang and McClugage have expressed it, the total area of the curve of increased calories. For the purposes of this present study, however, we were concerned with the presence and extent of the rise at whatever time it occurred and have thus chosen the highest point as the indication of the specific dynamic action, realizing that it is not a complete expression of the total effect of the meal. Stating that for a given person this figure was 27.1 per cent, we mean a maximum rise of 27.1 per cent over his resting or basal level occurring at a definite time during the test, i. e., at the end of one, two, three or four hours.

It is obvious that since this figure is derived from a basal level that may be either above or below a fixed average, it will be significantly influenced by the numerical value of that basal level. Thus, in a patient whose basal metabolism is —20, a rise of 10 calories per square meter per hour will result in a higher percentage increase than if his basal metabolism is +20. An analogy may be drawn to a stock market transaction. If a stock which is bought at $60 rises 40 points the profit will be twice that of a stock purchased at $120 with a similar rise in value. One must keep these points in mind in comparing the figures for the chromophobe group in which the basal metabolism was below normal in all but four instances with those of the acromegalic group in which the basal rate commonly was elevated. In similar manner, the smaller the surface area the greater will be the percentage increase when the figures are in terms of calories per square meter per hour.

As a matter of fact, it makes little actual difference whether the results of the test are expressed in the percentage above and below normal according to calories per square meter per hour or as total calories per hour. For instance, in table 1, case 1, with a surface area of 1.92 square meters, the specific dynamic rise by the one method is 27.1 per cent, by the other 27.6 per cent. In case 3 with a surface area of 1.7 square meters, the figures by the two methods of calculation are 25.9 compared with 26. For the purpose of record, the height, weight and surface area have been noted in the tables from which, if desired, the total calories per hour can be readily calculated for purposes of comparison. The reader is referred to the article of Strang and McClugage for a fuller discussion of what they term artificial influences on the calculations in a study of this type.

RESULTS

1. *Acromegaly (Hyperpituitarism).*—As noted earlier in the paper, the eighty-two patients have been divided into five groups according to the diagnosis. In table 1 are listed the findings on the fourteen patients with typical acromegaly. In four of these chromophil adenoma was surgically verified. One patient (case 3) had a mixed adenoma and one (case 12), a cystic adenoma; one patient is included in whom the acromegaly was thought to be a part of a polyglandular syndrome. Eight of them received roentgen treatments either supplementary to, or in place of, an operation. There are two points to which special attention should be called.

(*a*) Specific Dynamic Action: When expressed as the highest percentage increase over the basal metabolism, this varied from 6.5 to 38.7 per cent, the average rise being 19.0 per cent. Among those whose metabolism was studied for four hours, two showed the highest rise at the end of the first hour, two at the end of the second and three each at the end of the third and fourth hours. All of the patients showed a definite response to the protein meal.

(*b*) Basal Metabolism: It is known that in acromegaly not only is the basal metabolism usually elevated, but it also becomes lowered following either hypophyseal irradiation or operative excision of the pituitary adenoma. The figures in table 1 confirm these points. The

TABLE 1.—*Patients with Acromegaly*

Case	Age	Sex	Date	Height, Cm.	Weight, Kg.	Surface Area, Sq.M.	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak					
								1 Hour	2 Hours	3 Hours	4 Hours		
1	28	M	10/28/30	169.5	79.7	1.92	+ 7	+36	+21	+29	+31	27.1	102 Gm. of beefsteak; definite acromegaly; small sella
2	29	M	10/23/30	172.0	69.1	1.81	— 2						
			10/27/30	.....	68.9	1.81	— 3	+18	+16	+25	+12	26.8	178 Gm. of beefsteak; early definite acromegaly
			11/ 6–7/30										
			12/17–23/30	.....	....	....	Roentgen treatments						
			12/22/30	.....	61.3	1.72	+23	....	....	....	....	....	? Faulty determination
3	46	F	8/10/26	157.0	61.9	1.62	+19	....	....	....	....	....	Typical acromegaly
			8/12/26	.....	61.0	1.61	+17						
			8/16/26	.....	....	....	Operation	....	....	....	....	....	Transphenoidal; extirpation of verified adenoma
			9/10/26	.....	58.8	1.59	+ 9						
			9/23/26	.....	59.2	1.59	+ 4						
			8/24/27	.....	66.3	1.67	+ 5						
			8/25/27	.....	....	....	Roentgen treatments						
			10/ 4/27	.....	65.3	1.66	+ 1						
			10/4–6/27	.....	....	....	Roentgen treatments						
			10/ 7/27	.....	65.3	1.66	— 6						
			10/12/27	.....	65.3	1.66	— 4						
			12/12–17/27	.....	....	....	4 roentgen treatments						
			12/13/27	.....	65.1	1.67	+24	....	....	....	....	....	Slight glycosuria
			4/ 5/29	.....	68.9	1.70	— 4	— 1	+16	....	....	20.8	
			8/12/30	.....	68.5	1.70	— 15	+ 7	+ 1	— 1	— 5	25.9	120 Gm. of beefsteak
4	36	M	6/23/26	167.0	73.2	1.82	+16	....	....	....	....	....	Typical acromegaly
			7/ 2/26	.....	....	....	Operation	....	....	....	....	....	Transphenoidal; partial removal of chromophil adenoma
			7/12/26	.....	68.2	1.76	+ 3						
			9/25/26	.....	73.8	1.82	+ 2	....	....	....	....	....	Marked postoperative recession of symptoms
			3/22/28	.....	74.8	1.83	0	+ 9	+24*	....	....	24.0	
5	48	F	9/11/30	167.8	77.2	1.87	+ 5	+ 5	+13	+18	+25	19.1	Typical marked acromegaly; symptoms stationary; small sella
6	24	F	1/16/29	166.0	63.7	1.71	— 1						
			1/28/29	.....	64.9	1.72	— 2	+16	+16	....	....	18.4	
			5/21/29	.....	75.1	1.83	+13	+25	+27	....	....	11.0	
			5/31–6/3/29	.....	....	....	4 roentgen treatments						
			6/ 6/29	.....	74.4	1.82	0						
			11/ 8/29	.....	69.2	1.76	0	+ 7	+ 7	+16	+28	28.0	
			11/12–18/29	.....	....	....	4 roentgen treatments						
			1/28/30	.....	66.4	1.74	— 6	....	....	....	....	....	Acromegaly ? surgically unverified
			2/18–21/30	.....	....	....	4 roentgen treatments						
			5/21/31	.....	79.5	1.67	— 5	....	....	....	....	....	Polyglandular syndrome

7	53	F	6/23/30	168.5	82.3	1.93	+11	+25	+29	+22	+26	16.4	Marked acromegaly surgically unverified
			6/25-28/30	.....	....	....	Roentgen treatments						
			5/28/31	.....	85.1	1.97	+11						
			6/ 2-5/31	.....	....	....	4 roentgen treatments						
			6/ 6/31	.....	83.6	1.93	+20						
8	39	M	1/ 6/30	178.2	81.5	2.00	+24	+24	+28	+44	+37	16.1	Acute acromegaly, huge intracranial extension; chromophil adenoma verified at autopsy
9	48	F	2/12/29	169.4	74.3	1.85	+28						
			2/13/29	.....	74.2	1.85	+18	+36	+19	....	....	15.2	Advanced acromegaly
			2/20-28/29	.....	....	....	4 roentgen treatments						
			2/23/29	.....	74.5	1.85	+10						
			6/13/29	168.2	72.0	1.82	+15	+21	+36	....	....	18.2	
			6/24/29	.....	....	....	Hysterectomy						
			7/13/29	.....	65.6	1.75	+14						
			10/ 3/30	.....	67.2	1.75	+11	+17	+34	+20	+43	19.0	
10	35	F	10/20/27	168.0	82.6	1.93	+27	....	....	....	....	....	Typical acromegaly
			10/22/27	.....	82.2	1.93	+17						
			10/25/27	.....	....	....	Operation	....	....	....	....	....	Transphenoidal; evacuation of soft chromophil adenoma
			11/14/27	.....	80.2	1.90	+28						
			11/14-17/27	.....	....	....	4 roentgen treatments						
			5/26/28	.....	85.3	1.96	+15	+32	+27*	....	....	14.8	140 Gm. of beefsteak
11	26	F	3/ 7/29	181.3	91.4	2.13	+19	+33	+36	....	....	14.3	Typical outspoken acromegaly surgically unverified
12	24	M	12/ 9/30	197.0	88.3	2.23	+13	+17	+29	+25	+27	14.2	144 Gm. of beefsteak
			12/19/30	.....	....	....	Operation	....	....	....	....	....	Transfrontal; radical extirpation
			1/ 2/31	.....	84.7	2.18	7	+ 2	— 1	+29	+18	38.7	of cystic adenoma; outspoken
			1/ 9/31	.....	83.9	2.17	— 1						acromegalic gigantism; excellent surgical results
13	40	M	8/22/14	177.0	....	....	Operation	....	....	....	....	....	Transphenoidal; partial removal of
			7/16/29	.....	96.0	2.13	+30						chromophil adenoma; typical
			7/19/29	.....	96.1	2.13	+37	+52	+39	....	....	10.9	advancing acromegaly
			7/24-29/29	.....	....	....	4 roentgen treatments						
14	48	M	8/ 9/28	168.5	90.3	2.01	+32						
			8/11/28	.....	....	....	+23	+28	+31	....	....	6.5	Typical advanced acromegaly
			8/15-18/28	.....	....	....	4 roentgen treatments						surgically unverified
			8/18/28	.....	89.7	2.00	+13	+26	+27	....	....	12.4	
			8/20/28	.....	89.4	2.00	+10	+15	+22	....	....	10.9	
			10/17-19/28	.....	....	....	Roentgen treatments						
			10/19/28	.....	88.4	1.99	+19						
Average												19.0	

* Metabolism after one and one-half hours.

average basal metabolism in the seventy-two patients reported on by Davidoff and Cushing [12] was + 18.6 per cent. If we take for comparison the basal determinations noted in table 1 prior to operation or irradiation, we find the average for the group to be 11.5 per cent. In seven of nine instances studied there was a definite lowering of the metabolism following operation or roentgen treatment.

2. *"Fugitive" Acromegaly.*—There were seven patients (table 2) who have been grouped under the heading of "fugitive" acromegaly.[14] These persons showed evidence of acromegalic changes, but the disease appeared no longer to be in the active stage. They all showed a normal or relatively low metabolism, and in the four patients operated on there was found a mixed type of pituitary adenoma.

(*a*) Specific Dynamic Action: Variations in the percentage rise above the basal metabolism in this group ran from 8.8 to 25.1, the average being 17.9 per cent. None of these patients studied for four hours after the beefsteak meal showed the maximum rise at the end of the first hour. Four showed it at the end of the second hour, one at the third and four at the fourth. Observations made on four different occasions with the patient in case 3 show the variation in the degree of rise that may be seen in one person from day to day. In the first test his metabolism rose from + 7 to + 28, an increase of 19.6 per cent. Three days later the change was from — 4 to + 24, an increment of 29.2 per cent. Following the administration of thyroid extract, the basal metabolism was + 26 and this rose to + 48 an hour and a half after the ingestion of beefsteak, or an 18.5 per cent rise in spite of the high basal level. On a subsequent admission three and one-half years later, the metabolism rose from + 16 to + 34 at the end of the second hour, which is an increase of 15.5 per cent above the basal calories. Mention will be made later on of these variations in the specific dynamic reaction observed in the same person on different occasions.

(*b*) Basal Metabolism: If we omit the determinations made on the patient in case 3 during the time that thyroid extract was given, we find the average basal metabolism for this group to be — 1.

3. *Chromophobe Adenoma (Hypopituitarism).*—The third and largest group (table 3) includes those with a chromophobe adenoma often associated with more or less marked evidence of pituitary insufficiency (hypopituitarism). There were thirty-two patients studied in this group, and in nearly all instances the tumor was verified at operation.

(*a*) Specific Dynamic Action: This varied, rising from 5 to 41.5 per cent above the basal metabolism, with an average of 23.1 per cent. That this average is slightly higher than the average in the two preceding groups is to be explained in part by the lower level of basal metabolism, as mentioned previously in methods of tabulation. The

TABLE 2.—*Patients with "Fugitive" Acromegaly*

Case	Age	Sex	Date	Height, Cm.	Weight, Kg.	Surface Area, Sq.M.	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak: 1 Hour	2 Hours	3 Hours	4 Hours		
1	38	F	3/19/30	171.5	68.2	1.80	−13	**− 2**	**+ 1**	**+ 9**	**+ 8**	25.1	
2	41	F	12/16/29	153.0	63.0	1.60	−11	− 7	+10	+ 3	+ 4	23.6	Mixed adenoma verified
			12/28/29	.....	....	....	Operation	....	....	....	....	....	Transfrontal radical extirpation
3	27	M	2/ 7/28	168.0	66.7	1.76	+ 7	+24	+28*	....	....	19.6	
			2/10/28	.....	66.8	1.76	− 4	+16	+24*	....	....	22.2	
			2/17/28	.....	....	....	Operation	....	....	....	....	....	Transfrontal; radical extirpation of mixed adenoma
			2/28/28	.....	65.0	1.74	+ 9						
			2/28-3/7/28	.....	Received 2 grains of thyroid 3 times a day								
			3/ 1/28	.....	64.6	1.73	+10						
			3/ 7/28	.....	63.4	1.72	+26	+49	+48*	....	....	18.5	
			3/13/28	.....	63.3	1.72	+18						
			11/ 6/31	.....	64.6	1.73	+21						
			11/ 7/31	.....	64.5	1.73	+16	+33	+34	+30	+27	15.5	189 Gm. of beefsteak
			11/21/31	.....	....	....	Operation	....	....	....	....	....	Transfrontal; extirpation of mixed adenoma
			12/ 5/31	.....	61.1	1.70	+ 5						
			12/12/31	.....	60.4	1.69	+ 2						
4	33	F	8/24/26	166.4	78.5	1.87	− 2						
			8/28/26	.....	....	....	Operation	....	....	....	....	....	Transphenoidal; partial extirpation of mixed adenoma
			9/ 9/26	.....	79.3	1.88	−10						
			2/ 7/27	.....	84.4	1.92	− 6						
			2/11/27	.....	....	....	−10						
			2/23-24/27	.....	....	....	2 roentgen treatments						
			4/25/30	.....	86.3	1.96	− 6	+ 3	+ 7	+ 8	+11	18.1	185 Gm. of beefsteak
5	53	M	4/23/30	154.8	65.3	1.64	− 2	**+ 1**	**+ 4**	**+ 1**	**+14**	16.3	
6	26	F	6/26/26	157.0	56.7	1.57	0						
			7/ 6/26	.....	....	....	Operation	....	....	....	....	....	Transphenoidal; radical extirpation of mixed adenoma
			7/21/26	.....	54.0	1.53	− 9						
			7/24/29	.....	58.7	1.58	−12						
			7/29/29	.....	58.7	1.58	+ 4	+ 6	+17	+13	+11	12.5	
			7/21/31	.....	65.4	1.66	− 3						
			7/22/31	.....	64.9	1.66	− 1	+ 7	+ 4	+ 7	+15	16.1	
7	26	F	3/ 7/30	156.7	73.8	1.74	+ 2	+ 2	+11	+ 3	+10	8.8	
			3/ 8/30	.....	73.5	1.74	+ 2	+ 7	+ 8	+ 7	+13	10.8	
			4/4-8/30	.....	....	....	Roentgen treatments						
Average												17.9	

* Metabolism after one and one-half hours.

TABLE 3.—*Patients with Chromophobe Adenoma*

Case	Age	Sex	Date	Height, Cm.	Weight, Kg.	Surface Area, Sq.M.	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak: 1 Hour	2 Hours	3 Hours	4 Hours		
1	56	M	1/15/30	171.8	83.2	1.97	−30	−16	−23	−15	− 1	41.5	
			1/28/30	.....	....	....	Operation	....	....	....	....	....	Transfrontal; extirpation of chromophobe adenoma
2	52	F	1/ 4/30	151.2	97.5	1.92	−21	−13	− 7	+ 1	+10	39.2	
			1/ 8/30	.....	97.7	1.92	−13	− 7	− 3	+ 1	+ 5	20.7	
			1/18/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 1
			12/ 8/30	.....	94.2	1.89	−13						
			12/10/30	.....	93.9	1.88	−18						
			12/17/30	.....	93.0	1.87	−19						
3	31	M	4/17/30	182.0	78.0	1.99	−24	− 9	− 8	+ 4	− 5	26.8	
			4/18/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 1
4	51	F	4/16/30	167.0	65.0	1.73	−23	+ 2	0	+ 5	+ 5	30.4	
			4/23/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 1
5	30	M	6/ 4/30	178.0	93.6	2.12	−17	− 6	+13	− 2	− 3	36.2	
			6/17/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 1
			6/27/30	.....	89.9	2.08	−14						
6	42	M	9/17/30	164.8	81.6	1.89	−22	−10	+ 3	+ 5	− 6	34.6	
			9/25/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 1
			10/ 4/30	.....	79.7	1.87	−11						
			10/17/30	.....	81.6	1.89	−22						
7	34	M	2/12/30	173.0	63.2	1.75	−31	−28	−15	−18	−10	30.4	
			2/24/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 1
8	44	F	6/21/28	167.5	59.8	1.68	−12						
			6/27/28	.....	....	....	Operation	....	....	....	....	....	Same as in case 1
			7/ 5/28	.....	61.2	1.69	−16						
			7/11/28	.....	59.0	1.67	−19	+ 4	+ 2*	....	....	28.4	
			7/23/28	.....	59.0	1.67	−25	−10	−11	....	....	20.0	
9	22	M	6/21/30	179.0	74.5	1.94	−22	− 7	− 1	− 7	− 6	26.9	Chromophobe adenoma unverified
10	35	F	10/11/28	154.7	55.3	1.53	−24	− 4	− 8	....	....	26.3	
			10/24/28	.....	....	....	Operation	....	....	....	....	....	Extirpation of chromophobe adenocarcinoma
11	23	M	2/14/25	.....	....	....	Operation	....	....	....	....	....	Transphenoidal; extirpation of chromophobe adenoma
			2/27/25	162.5	66.7	1.72	−33						
			4/18/25	.....	69.3	1.74	−28						
			2/15/29	.....	72.3	1.78	−25						
			2/25/29	.....	70.3	1.75	−27	−19	− 8	....	....	26.0	

12	42	M	7/16/30	172.7	73.9	1.88	−15	+ 7	−4	− 1	+ 6	25.9
			7/21/30	.....	....	....	Operation	....	....	....	....	....	Transfrontal; extirpation of chromophobe adenoma
13	42	M	1/ 3/30	165.6	83.6	1.91	−10	− 2	+ 5	+ 8	+11	23.4
			1/15/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 12.
14	42	F	5/21/30	170.0	75.3	1.86	−18	−15	− 9	− 2	+ 1	23.1
			5/28/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
			6/21/30	.....	75.3	1.86	−25						
			6/26/30	.....	75.3	1.86	−29						
15	25	F	8/25/27	157.5	66.5	1.68	−16						
			8/30/27	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
			9/15/27	.....	65.4	1.67	−20						
			1/16/29	....	67.1	1.69	−21	− 9	− 3	....	....	22.8	
16	39	M	6/ 6/28	163.0	66.5	1.72	− 9						
			6/19/28	.....	68.0	1.75	−10	− 3	+10	....	....	22.2	
			6/22/28	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
			7/ 5/28	.....	64.4	1.70	−16						
			7/ 6/28	.....	64.9	1.71	− 2	+15	0	....	....	11.7	? Faulty observation
17	36	M	8/ 2/29	174.4	73.5	1.89	−26						
			8/ 7/29	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
			9/ 6/29	.....	69.4	1.83	−44						
			2/21/30	.....	63.8	1.77	−34						
			2/27/30	.....	65.0	1.78	−37	−29	−24	−23	−29	22.2	
			6/16/31	.....	70.3	1.84	−33						
18	50	F	7/21/30	159.5	58.6	1.60	− 9	+ 2	− 7	+ 5	+11	22.0	
			8/19/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
19	29	F	10/10/29	153.6	49.6	1.45	−16	−10	0	+ 2	− 8	21.4	
			10/28/29	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
20	26	M	1/13/30	171.6	72.7	1.85	−24	−20	− 8	−12	−13	21.0	
			1/23/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
21	51	F	1/ 2/29	178.0	56.2	1.71	−16						
			1/18/29	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
			2/ 8/29	.....	53.0	1.61	−27						
			2/15/29	.....	54.1	1.63	−28	−22	−13	....	....	20.8	
22	23	F	2/24/30	151.2	51.3	1.46	−21	−13	− 3	−10	− 5	20.1	
			3/ 5/30	.....	51.7	1.46	−25	−18	− 8	− 8	− 2	30.6	
			3/ 6/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
			4/ 8/30	.....	48.5	1.41	−22						
23	22	M	12/ 5/29	164.2	54.4	1.58	−20	− 8	−15	− 8	− 4	20.0	
			12/ 9/29	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
24	67	M	5/10/30	175.2	68.2	1.83	− 8	− 5	+ 7	− 2	+ 9	18.5	
			5/19/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 12
			6/ 9/30	.....	62.0	1.76	−22						
			6/11/30	.....	59.6	1.73	−24						

* Metabolism after one and one-half hours.

TABLE 3.—*Patients with Chromophobe Adenoma—Continued*

Case	Age	Sex	Date	Height, Cm.	Weight, Kg.	Surface Area, Sq.M.	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak: 1 Hour	2 Hours	3 Hours	4 Hours		
25	44	M	10/28/26	176.8	83.8	2.01	+21						
			11/ 5/26	.....	....	....	Operation	....	....	....	....	....	Transphenoidal; chromophobe adenoma, possibly of mixed type
			11/26/26	175.6	73.8	1.90	— 5						
			9/20/30	.....	90.3	2.07	0	+16	+11	+17	+16	17.0	146 Gm. of beefsteak
			9/22/30	.....	....	....	Operation	....	....	....	....	....	Transfrontal; recurrence of adenoma of same type
			10/ 3/30	.....	86.7	2.04	—12						
			10/ 7/30	.....	89.0	2.06	—10						
26	66	F	5/19/30	166.0	49.4	1.53	—10	—11	— 3	+ 1	+ 4	15.6	
			5/24/30	.....	....	....	Operation	....	....	....	....	....	Transfrontal; extirpation of chromophobe adenoma
			6/19/30	.....	50.1	1.54	—26						
27	35	F	8/ 7/30	160.0	87.7	1.91	+ 2						
			8/ 9/30	.....	87.7	1.91	+ 4	+15	+17	+20	+19	15.4	110 Gm. of beefsteak
			8/12/30	.....	....	....	Operation	....	....	....	....	....	Radical removal of cystic adenocarcinoma
28	50	M	7/ 5/28	182.0	74.2	1.95	—26						
			7/ 7/28	.....	73.3	1.94	—22	—18	—10	....	....	15.4	
			7/11/28	.....	....	....	Operation	....	....	....	....	....	Transfrontal; extirpation of chromophobe adenoma
			7/25/28	.....	72.6	1.93	—28						
			1/ 5/32	.....	75.0	1.95	—25						
			1/ 6/32	.....	75.0	1.95	—30	—23	—25	—23	—17	18.2	
29	18	M	7/21/28	165.0	63.5	1.70	— 7						
			7/23/28	.....	63.5	1.70	—16						
			8/ 1/28	.....	....	....	Operation	....	....	....	....	....	Same as in case 28
			8/11/28	.....	56.8	1.63	—19						
			8/15/28	.....	59.1	1.65	—20	—14	— 8	....	....	15.0	
30	45	F	2/20/30	157.5	87.3	1.88	—11	— 8	+ 1	— 2	— 2	13.5	150 Gm. of beefsteak
			3/ 1/30	.....	....	....	Operation	....	....	....	....	....	Same as in case 28
			3/18/30	.....	80.5	1.81	— 8						
			3/29/30	.....	79.1	1.79	— 5						
31	37	M	9/24/27	160.2	68.8	1.72	—23						
			10/ 1/27	.....	68.6	1.72	—12						
			10/ 4/27	.....	....	....	Operation	....	....	....	....	....	Same as in case 28
			10/18/27	.....	67.1	1.70	—10						
			10/20/27	.....	66.9	1.70	— 5						
			4/20/28	.....	66.5	1.69	— 6	+ 3	+ 5*	....	....	11.7	100 Gm. of beefsteak
32	30	M	11/26/28	169.0	57.0	1.65	—26	....	....	....	....	....	Marked hypopituitarism
			12/ 4/28	.....	....	....	Operation	....	....	....	....	....	Chromophobe adenoma with hemorrhagic cyst; partial evacuation
			12/31/28	.....	53.9	1.61	—26						
			1/ 4/29	.....	54.3	1.61	—30	—24	—24*	....	....	5.0	
Average							—19	....	....	....	....	23.1	

* Metabolism after one and one-half hours.

time of the "peak" of metabolism increase in this group is of interest because it occurs in most instances late in the period of observation. Of twenty-five patients studied for four hours after the meal, only one showed a peak at the end of the first hour, five at the end of the second hour, seven at the third and twelve at the fourth. Further comments on this point will be made later in the discussion. It is in this group of patients with diminished pituitary function that one should find a lessened response to the stimulation of a protein meal if the contention is true that the hypophysis influences the specific dynamic action of food. Not only was there a definite increase in the metabolism in each instance in this group, but the average increase was higher than any of the other groups of patients with pituitary disorders.

(*b*) Basal Metabolism: As previously pointed out,[12] the basal metabolism in patients with this type of pituitary adenoma is usually at a low level. With only four exceptions, all of the eighty-three determinations of the basal metabolism were below zero, and sixty-four (77.1 per cent) of them were less than — 10. The average for the entire group was — 19.

4. *Patients with Parahypophyseal Tumors.*—There were sixteen patients studied (table 4) in whom many features suggested, early in their course, a disturbance of pituitary origin. These were found later either at operation or by further clinical study to have, not a primary pituitary disorder, but a lesion in the region of the hypophysis producing secondarily the picture of pituitary insufficiency. In many respects, then, they were similar to the preceding group with chromophobe adenomas. There were five with tumor of the third ventricle, three with craniopharyngioma, two with suprasellar meningioma, two with suprasellar cyst, one with a willisian aneurysm, and three in which an anatomic diagnosis was not made.

(*a*) Specific Dynamic Action: Variations in the percentage rise in this group ran from 9.6 to 35.5, the average being 20.4. Two showed the maximum rise at the end of the first hour, one each a the end of the second and third and eight at the end of the fourth.

(*b*) Basal Metabolism: As in the group with chromophobe adenomas, the basal metabolism was distinctly lowered, the average being — 17 with twenty-five of thirty-seven determinations (67 per cent) registering below — 10.

5. *Control Group.*—The test was carried out on thirteen patients (table 5) who were shown subsequently not to have a pituitary tumor or any definite lesion in the vicinity of the hypophysis. This group serves as a control on the others. In the column of "comment" one may see the wide variety of conditions represented among these thirteen patients.

TABLE 4.—*Patients with Parahypophyseal Tumors*

Case	Age	Sex	Date	Height, Cm.	Weight, Kg.	Surface Area, Sq.M.	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak					
								1 Hour	2 Hours	3 Hours	4 Hours		
1	50	F	10/ 9/29	153.6	52.9	1.49	—24	— 6	— 1	— 2	+ 3	35.5	Hypertension; willisian aneurysm unverified
2	41	M	4/14/30	171.0	83.1	1.95	—13	— 4	+11	+13	+17	34.5	Hypertension; adiposity; bitemporal hemianopia
3	48	F	8/23/28	162.6	59.9	1.64	—14						
			8/25/28	.....	59.0	1.63	—15	+13	+14	....	....	33.0	
			9/21/28	.....	....	....	Operation	....	....	....	....	....	Suprasellar meningioma
4	24	M	4/14/26	167.5	55.5	1.63	—26						
			7/12/26	.....	56.7	1.65	—28	....	....	....	....	....	Craniopharyngioma verified
			3/16/27	.....	57.9	1.65	—30						
			3/22/30	.....	63.7	1.73	—28	—11	— 8	—18	— 7	29.2	
5	16	F	1/11/26	158.0	27.2	1.04	—16						
			2/26/30	156.8	52.0	1.50	—13	+ 2	— 4	+ 4	+10	26.4	
			3/ 7/30	.....	....	....	Operation	....	....	....	....	....	Transventricular; extirpation of astroblastoma of third ventricle
			4/16/30	.....	51.4	1.49	—11						
6	46	M	10/ 5/28	177.6	86.0	2.03	—32						
			10/10/28	.....	86.0	2.03	—27	—10	—10	....	....	23.3	
			11/ 5/28	.....	....	....	Operation	....	....	....	....	....	Transfrontal; craniopharyngioma verified
7	25	M	7/20/29	136.5	31.2	1.09	—20						
			7/23/29	.....	31.7	1.10	—12	+ 3	+ 8	....	....	22.8	Pituitary dwarfism (Simon's)
8	10	F	2/23/28	138.5	40.1	1.23	—32						
			2/24/28	.....	40.3	1.23	—29	—14	—17*	....	....	21.2	Craniopharyngioma
			5/29/28	139.5	41.7	1.25	—23	+ 5	— 2*	....	....	36.4	
			6/ 1/28	.....	41.3	1.25	—27	—19	—19*	....	....	10.9	
			6/25/28	.....	....	....	Operation	....	....	....	....	....	Transfrontal; evacuation and partial removal of cyst
			7/ 6/28	140.0	38.3	1.22	—43	—30	—32	....	....	22.8	

9	36	M	4/21/30	168.2	66.5	1.76	−10	+ 4	+ 7	0	+ 7	18.9	
			4/22/30	.....	....	....	Operation	....	....	....	....	....	Transfrontal; suprasellar meningioma; total extirpation
10	29	M	3/12/30	175.1	70.5	1.85	− 9	+ 2	+ 7	+ 3	+ 8	18.7	Tumor of third ventricle, unverified
			3/31/30	.....	....	....	Operation	....	....	....	....	....	Bone flap and decompression not modifying condition
			4/30/30	.....	69.4	1.85	− 9	+ 5	+ 5	+ 2	+ 3	15.4	
11	12	M	4/18/30	157.0	56.0	1.55	−23	−21	−14	−14	−11	15.6	Adiposogenital dystrophy
12	21	M	3/26/30	175.6	106.1	2.21	− 6	+ 8	+ 5	− 2	+ 5	14.9	Adiposity; tumor of third ventricle suspected
13	23	F	5/ 1/28	164.0	98.4	2.05	+ 2	....	....	....	....	....	Adiposity; tumor of third ventricle suspected
			5/ 3/28	.....	98.0	2.04	− 1						
			1/ 7/31	.....	115.6	2.20	+ 2	+ 7	+ 9	+14	+16	13.7	132 Gm. of beefsteak
14	40	M	3/28/30	175.2	74.8	1.90	+ 1	+ 2	+ 3	+13	+12	11.9	Glioma of third ventricle verified
			4/ 5/30	.....	....	....	Operation						
15	37	M	2/ 3/28	174.0	68.0	1.82	−29	....	....	....	....	....	Marked hypopituitarism
			2/ 4/28	.....	67.6	1.81	−30	....	−23*	....	....	10.0	
			2/ 7/28	.....	....	....	Operation	....	....	....	....	....	Transfrontal; evacuation of degenerated cyst, possibly chondroma
			2/21/28	.....	65.1	1.79	−23	−19	−14*	....	....	11.7	
			2/25/28	.....	65.6	1.79	−24						
			2/29/28	.....	65.7	1.79	−10	+ 1	+ 2*	....	....	13.3	112 Gm. of beefsteak
			2/21-8/5	.....	Received 2 grains of thyroid 3 times a day								
			3/ 5/28	.....	62.5	1.75	− 2						
			3/ 9/28	.....	62.7	1.76	+11						
16	22	M	1/21/31	167.5	80.9	1.91	+ 4	+ 9	+11	+11	+14	9.6	Suprasellar inflammatory cyst
			1/29/31	.....	....	....	Operation						
Average							−17	....	....	....	....	20.4	

* Metabolism after one and one-half hours.

TABLE 5.—*Control Group of Patients*

Case	Age	Sex	Date	Height, Cm.	Weight, Kg.	Surface Area, Sq.M.	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak: 1 Hour	2 Hours	3 Hours	4 Hours		
1	53	M	5/17/30	166.3	61.0	1.68	—34	—18	+ 2	—15	— 7	54.5	140 Gm. of beefsteak
			5/22/30	.....	....	....	Operation	....	....	....	....	....	Occipital glioma verified
2	9	F	2/28/28	133.4	27.5	1.01	—29	....	....	....	....	....	Cerebral tumor unverified
			3/ 2/28	.....	27.1	1.00	—20	+ 6	+ 5	....	....	32.5	
3	33	F	11/ 1/26	171.0	76.0	1.88	—10	....	....	....	....	....	Obscure polyglandular disorder
			12/24/28	.....	80.5	1.93	—10						
			11/30/29	.....	81.9	1.94	—15	—14	0	0	+10	29.4	
4	13	F	3/13/30	154.5	57.4	1.55	—18	— 2	+ 1	+ 2	+ 4	26.8	165 Gm. of beefsteak; angiomatosis of retinas
5	60	F	2/19/30	154.0	59.3	1.57	— 1	+16	+23	+23	+17	24.2	120 Gm. of beefsteak; osteitis deformans
6	28	F	6/ 5/30	168.1	62.3	1.71	—17	— 1	— 3	+ 3	— 3	24.1	Hydrocephalus; cerebral tumor unverified
			9/ 4/30	.....	67.9	1.77	—18	+ 3	+ 1	0	+10	34.2	120 Gm. of beefsteak
7	47	M	12/ 9/29	176.0	105.1	2.21	—12	+ 3	+ 1	+ 6	+ 3	20.4	Vasomotor instability
8	37	M	12/11/29	171.0	132.5	2.38	+18	+33	+37	+39	+36	17.8	Intracranial tumor unverified
9	30	M	8/13/30	184.2	86.8	2.10	—10	— 1	— 1	0	+ 4	15.5	Obscure endocrinopathy; adiposity with glycosuria
10	39	F	2/ 3/31	150.5	55.8	1.51	+ 3	+12	+ 3	+18	+16	14.5	146 Gm. of beefsteak
			2/ 9/31	.....	....	....	Operation	....	....	....	....	....	Meningioma
			10/28/31	.....	59.4	1.54	— 3						
			10/31/31	.....	59.4	1.54	— 5	+15	+19	+26	+24	32.6	
11	30	M	12/14/29	179.6	64.0	1.81	— 4						
			12/19/29	.....	64.2	1.81	—10	— 5	— 7	0	— 2	11.1	Chronic meningitis
12	13	F	10/25/29	180.4	67.2	1.85	—19	—10	—21	—16	—15	11.1	Obscure endocrinopathy
13	15	F	5/ 3/28	158.0	98.0	1.99	+ 1						
			5/10/28	.....	97.3	1.97	— 6	....	....	....	....	....	Adipositas cerebralis ?
			6/28/28	.....	95.1	1.96	— 1						
			6/30/28	.....	95.5	1.96	— 6	— 4	— 4	....	....	2.1	
Average							—10	....	....	....	....	23.4	

(*a*) Specific Dynamic Action: The average percentage increase here was 23.4, with 2.1 and 54.5 as extremes. This is the highest average rise of any of the groups, though it differs by only 0.3 per cent from that found in patients with chromophobe adenomas, and is to an extent influenced by the low average basal metabolism of — 10. The peak of metabolism increase was again found to occur more commonly after the third or fourth hour, ten of the four hour tests showing the highest rise at this time as compared with two after the second hour and one after the first.

(*b*) Basal Metabolism: There is little of note concerning this, excepting the extremes of — 34 and + 18, with — 10 as the average for the group.

COMMENT

This study is reported to show the effect of a protein meal on the metabolism of patients with pituitary disease. In the foregoing statements of results the essential facts are presented. They may be summarized briefly in table 6. These figures show that in patients with pituitary disorders there is an increased heat production of essentially the same magnitude as that found in normal persons by other workers.[17] In other words, a disturbance of pituitary function, whether due to either of the usual types of pituitary adenomas or to pressure on the hypophysis from an adjacent tumor, does not have any influence one way or the other on the metabolic response to a protein meal. The large mass of data presented here affords at least that answer to the question: Does the pituitary gland have any direct bearing on the specific dynamic action of food?

TABLE 6.—*Effect of Protein Meal on Metabolism in Pituitary Disease*

Group	Number of Patients	Average Basal Metabolism	Average Highest Percentage Increase in Metabolism after Beefsteak Meal
I. Acromegaly	14	+11.5	19.0
II. Fugitive acromegaly	7	— 1.0	17.9
III. Hypopituitarism	32	—19.0	23.1
IV. Parahypophyseal tumor	16	—17.0	20.4
V. Control	13	—10.0	23.4
Average			20.7

There are one or two further points in this study to which attention may be called. The first is the variation in the degree of rise in metabolism after food that may be seen in the same person from day to day. Whereas, in some instances this is found to be relatively constant (as

17. Wang, C. C.; Strause, S., and Saunders, A. D.: Studies on the Metabolism of Obesity: III. The Specific Dynamic Action of Food, Arch. Int. Med. **34**:573 (Oct.) 1924. Strang and McClugage.[15]

in cases 6 and 7, table 2, and cases 10 and 15, table 4), in others there is considerable difference in the extent of the rise on repeated tests. The following are examples of this among the persons on whom more than one four hour test was carried out (table 7).

In part, these differences in the percentage increase of metabolism are due to differences in the basal metabolism on the two days which give an artificial magnification to the increased heat production. Strang and McClugage found a similar variation in the response to food in some of their well trained patients who had repeated tests. It is entirely probable that the total heat production in our patients measured

TABLE 7.—*Data on Patients Given More Than One Four Hour Test*

Patient	Date	Basal Metabolism	Percentage Increase after Beefsteak Meal
Case 13 (table 1)	12/ 9/30	+13	14.2
	1/ 2/31	— 7	38.7
Case 2 (table 3)	1/ 4/30	—21	39.2
	1/ 8/30	—13	20.7
Case 22 (table 3)	2/24/30	—21	20.1
	3/ 5/30	—25	30.6
Case 6 (table 5)	6/ 5/30	—17	24.1
	9/ 4/30	—18	34.2
Case 10 (table 5)	2/ 3/31	+ 3	14.5
	10/31/31	— 5	32.6

TABLE 8.—*Peak of Metabolism Rise at Different Intervals*

Group	1 Hour	2 Hours	3 Hours	4 Hours
I. Acromegaly	2	2	3	3
II. Fugitive acromegaly	0	4	1	4
III. Hypopituitarism	1	5	7	12
IV. Parahypophyseal tumor	2	1	1	8
V. Control	1	2	6	4
Total	6	14	18	31

over a period of eight hours would not show any such variation as is suggested by the change in percentage increase of metabolism on different days. It has been shown by several observers[18] that there is no appreciable difference in the total heat effect of a meal as observed when repeated tests are done on the same person.

A second point is the time of the "peak" of metabolism rise in this series of patients. This has been noted previously for each group. In summary, the figures are as shown in table 8.

In the sixty-nine four hour tests carried out, we find the highest metabolism at the end of three or four hours in forty-nine, or 71 per

18. Lauter, S.: Zur Genese der Fettsucht, Deutsches Arch. f. klin. Med. **150**: 315 (March) 1926. Strang and McClugage.[15]

cent. This is in keeping with the studies reported by others,[19] which show that after a meal consisting mainly of protein, the highest metabolism is most commonly found during the third and fourth hours. Strang and McClugage found the maximum response at an earlier time, but their test meal contained considerable carbohydrate which would have a more prompt effect on the metabolism. As they point out, the palatability of the food and its psychic effect on gastric secretion, the rate of emptying of the stomach and absorption of the digestion products from the intestine will all influence the speed of the metabolic response.

CONCLUSIONS

The specific dynamic action of protein was observed in fifty-three patients with pituitary disease, sixteen others with parahypophyseal tumors and thirteen control subjects. The metabolic response to the protein meal was essentially the same in all the groups and was well within the range of normal limits.

The study indicates that disturbance in pituitary function as seen in man has no influence on the specific dynamic action of protein. It lends further support to the view that the endocrine glands have no direct bearing on the specific dynamic action of food.

Miss Kathryn Weitzel and Miss Maude Lacey rendered technical assistance.

19. Gephart, F. C., and Du Bois, E. F.: Clinical Calorimetry: IV. The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. **15**:835 (May) 1915. Mason, E. H.; Hill, E., and Charlton, D.: Abnormal Specific Dynamic Action of Protein, Glucose, and Fat Associated with Undernutrition, J. Clin. Investigation **4**:353 (Aug.) 1927. Aub and Means.[7]

EFFECT OF DIGITALIS ON THE CORONARY FLOW

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The effect of digitalis on the coronary vessels or on the volume of coronary flow has received a very moderate amount of attention. The clinical and experimental evidence for or against any change in coronary flow with the administration of digitalis has been conflicting and not altogether convincing.

Clinical observation of the effect of digitalis cannot be adequately controlled, and there is always the possibility that a favorable or untoward result following the administration of digitalis might equally have ensued if the drug had not been given. When the effect of digitalis on auricular fibrillation, on minute volume output or on edema is considered, one has measurable results to record. This is not possible in the case of the effect of digitalis on coronary flow.

Our own clinical experience led us to believe that untoward effects might occur with the use of digitalis in coronary disease, and that these effects might be due to coronary vasoconstriction.

Experimental work has previously been done to ascertain the effect of digitalis on arterial strips, on the isolated heart and on preparations of the intact animal. Cow,[1] using arterial strips, found evidence of vasodilatation of the coronary artery when watery solutions of digitalis were added to the solution in which the artery strip was suspended. Strips of other arteries contracted under the same conditions. Voegtlein and Macht,[2] Eppinger and Hess,[3] Rabe[4] and others have shown a contraction of arterial strips from the coronary. Rabe[4] showed that strophanthin constricted the coronaries in a dilution of 1:20,000,000, while a dilution of 1:1,000 showed either no effect or only a slight effect on peripheral vessels. Digitalin constricted the coronary arteries in a 1:5,000,000 dilution, but constriction of the peripheral vessels

From the Medical Department of Northwestern University and St. Luke's Hospital.

1. Cow: J. Physiol. **42**:125, 1911.
2. Voegtlein and Macht: J. Pharmacol. & Exper. Therap. **77**:5, 1913.
3. Eppinger and Hess: Ztschr. f. exper. Path. u. Therap. **5**:622, 1908.
4. Rabe: Ztschr. f. exper. Path. u. Therap. **11**:175, 1912.

occurred only in a 1 : 10,000 dilution. The results of experiments by the same author on the effect of other drugs on arterial strips agree with other experimental and clinical observations, and, in spite of certain objections to the method, we feel that the results are significant.

The results obtained by various workers on the isolated heart show preponderantly that there is a vasoconstrictor action on the coronary arteries by digitalis. Cushny [5] objected to drawing any conclusions from results obtained on the isolated heart because of the frequent changes in the activity of the heart during the experiment, and also because of the use by the investigators of concentrations of the drug in excess of those that would be administered clinically. Meyer [6] stated that in the isolated heart there is only a short second stage during which pharmacologic experiments are of any value.

Our own unpublished experiments with this method would tend to confirm the objections of Cushny and of Meyer. By perfusion with oxygenated Locke's or Ringer's solution, we obtained striking evidence of coronary vasoconstriction with concentrations of the drug comparable to or less than those used therapeutically.

When oxygenated heparinized whole blood was used as a perfusing solution, similar small doses failed to give conclusive results. In addition, an empty beating heart allowed to beat for long periods under constant conditions without any experimental interference shows so many spontaneous variations as to render doubtful any results obtained with drugs.

Bodo,[7] using the heart-lung preparation, in which venous inflow, pulse rate, peripheral resistance and blood pressure were controlled and constant, found a small increase in the coronary flow with digitalis. It is possible that the simultaneous use of a Henderson cardiometer influenced the results, as changes in tonus would alter the pressure of the cardiometer diaphragm.

There have been comparatively few experiments on the intact animal. Bond [8] suspended a cat face downward with the apex of the heart held in position by a suture. A cut was made in a coronary vein, and the drops were counted as they fell. He found no change in flow to result from digitalis administration. Meyer,[6] in curarized cats, passed a cannula into a superficial vein and measured the flow. He found an increase in flow with digitalis bodies. It is possible that the effect of the curare on the sympathetic ganglion may have influenced his results.

5. Cushny, Arthur: Digitalis and Its Allies, New York, Longmans, Green & Co., 1925.

6. Meyer, F.: Arch. f. Physiol., 1912, p. 223.

7. Bodo, R.: J. Physiol. **64**:365, 1928.

8. Bond: J. Exper. Med. **12**:575, 1910.

Sakai and Saneyoshi[9] performed their experiments on the intact animal, using cats under ethyl carbamate (urethane) anesthesia. A Morovitz cannula was passed through the auricular appendage into the coronary sinus, and the flow was measured. They found a vasoconstrictor effect from large doses of strophanthin, but with doses approximating those used clinically the coronary flow followed the blood pressure without evidence of vasoconstriction or of vasodilatation.

METHOD

We conducted our own experiments on the intact animal with a preparation very similar to that of Sakai and Saneyoshi. A short experience with the use of single doses of varying size convinced us that results obtained by this method are of small value. In the intact animal, even with conditions such as venous return, temperature, etc., kept constant, there still remain variations in pulse and blood pressure that vitiate the results from the administration of single doses. To attempt to obviate these difficulties we decided to use a large number of dogs, and to make first a control series of experiments in which the variations in coronary flow under standard conditions were observed over a period of from one and a half to two hours without the use of any medication. Similar series of tests were then made under identical conditions, but with fractions of the estimated lethal dose of digitalis administered at regular intervals until death. A comparison of the results in the control series and in the series in which digitalis was administered should throw some light on the effect of digitalis on the coronary flow.

The anesthetics used were diallylbarbituric acid, sodium barbital, chlorbutanol and the Grehant anesthetic (5 per cent chloroform in a solution of equal parts of alcohol and water). We could detect no difference in the effect of these.

The technic was the same as that previously reported by us.[10] The chest was opened in the midline and a modified Morovitz cannula passed through the right auricular appendage into the coronary sinus. The cannula was connected with the cylinder of a piston recorder, and the rise of fluid level in the cylinder traced on a revolving drum. With a known capacity of the cylinder of the piston recorder, the volume of the coronary flow was readily estimated by measurement of the rise of the line traced on the drum.

The blood was returned to a jacketed cylinder kept at a constant temperature and connected with the femoral vein. The height of the cylinder was adjusted so as to admit of a volume of return flow approximately equal to the volume flowing out through the coronary cannula. The pressure remained constant throughout the experiment, and was not changed to meet variations in venous pressure. The fluid level in the return flow cylinder was kept constant by a simple device that functioned automatically. The temperature of the animal and that of the return flow were constant for the experiment.

Blood pressure was recorded from the carotid artery by a mercury manometer. The experiment was not started until the preparation had become stabilized, the return flow was adjusted to meet the volume of blood flow from the coronary sinus, and blood pressure and pulse rate were at an almost constant level.

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9. Sakai and Saneyoshi: Arch. exper. Path. u. Pharmakol. **78**:331, 1914.

10. Gilbert, N. C., and Fenn, G. K.: The Effect of the Purine Base Diuretics on the Coronary Flow, Arch. Int. Med. **44**:118 (July) 1929.

Such an experiment establishes obviously abnormal conditions, but comes as close to normal conditions as any method that we know of for measuring coronary flow. The trauma of the operation and that of the cannula in the sinus offer many variables, but they are constant for the experiment. During the experiment there is a progressive shift of the hydrogen ion concentration of the blood toward the acid side, but this and any increase in metabolites would tend to increase rather than to diminish the coronary flow. Whatever the variables may be, they prevail equally in the control series. Concerning the anesthetic, it may be asked whether such a traumatized animal under full anesthesia offers more variables in the way of vasodilator and vasoconstrictor reflexes than a conscious, normal animal in which the reflex pathways to the coronary arteries are open to stimuli from a multitude of sources.

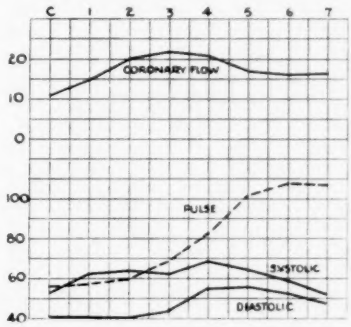

Chart 1.—Results of a single experiment on a control animal (dog 46), in which the course of the coronary flow, systolic and diastolic pressure and pulse rate were observed and recorded over a period of time comparable to that in the experiments in which digitalis was used. In this and in all subsequent charts the abscissas represent fluctuations in coronary flow, blood pressure and pulse rate. The ordinates indicate the control reading, represented by (*C*) and the subsequent readings at ten minute intervals. The upper curve represents the coronary flow in cubic centimeters per minute, charted at ten minute intervals. Readings of the blood pressure in millimeters of mercury, and of the pulse rate in beats per minute, are charted at the corresponding intervals.

The fact that blood pressure was not controlled would have rendered the whole series, even with the control experiments, of much less value had it not been that there was a certain proportion of cases in which digitalis was used and in which the coronary flow decreased with digitalis in spite of an increase in systolic and diastolic pressure and in pulse rate. It is only such cases in which we have assumed that digitalis exerted a vasoconstrictor action. It is quite possible, but not proved, that there was a vasoconstrictor action in at least part of the cases in which either blood pressure or pulse rate decreased.

CONTROL SERIES

The coronary flow was measured over a period of from one and one-half to two hours under the same standard conditions in which the effect of digitalis was observed. Ten dogs were used, and at the conclusion of the experiments with digitalis three more were added in order to determine whether the results conformed to those obtained earlier. The results of a typical control series are plotted in charts 1 and 2. The volume of coronary flow in cubic centimeters per minute, the systolic and diastolic pressure in millimeters of mercury and the pulse rate at ten minute intervals are plotted. In chart 1, the coronary flow is shown to rise with the blood pressure and pulse rate for the first ten minutes. In the next ten minutes the coronary flow continues

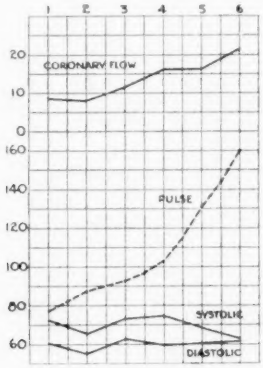

Chart 2.—Results of a second control experiment (dog 48), in which the coronary flow and its determining factors follow a somewhat different course.

to rise, with a falling systolic and an almost level diastolic pressure, but with a rising pulse rate. In chart 2 is also seen evidence of the effect of the pulse rate on the coronary flow. Smith [11] has reviewed the effect of the pulse rate on the volume of coronary flow and has given the results of his own work on the isolated heart. He expressed the belief that reduction and acceleration of the cardiac rate within certain limits are associated with definite changes in the rate of coronary flow. Our experience in this work confirms this, and we feel that the pulse rate must be considered as a factor in the volume of coronary flow.

11. Smith, F. M.: The Coronary Circulation, Arch. Int. Med. **40**:281 (Sept.) 1927.

The results of the control series are summarized as follows:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	2
Increase in coronary flow accounted for by rise in blood pressure or pulse rate	11

It will be observed that there was no decrease in coronary flow that could not be accounted for by a fall in systolic or diastolic pressure or pulse rate, and that the volume of coronary flow followed changes in these factors. If we assume that the volume of coronary flow is a function of diastolic and systolic pressure only, disregarding the effect of the pulse rate, the results are as follows:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure	1
Decrease in coronary flow accounted for by fall in blood pressure	1
Increase in coronary flow accounted for by rise in blood pressure	7
Increase in coronary flow unaccounted for by rise in blood pressure	4

Here there appears a decrease in coronary flow that is not accounted for by a fall in blood pressure, but there also appear four cases in which there was an increase in coronary flow without an underlying rise in blood pressure.

EFFECT OF DIGITALIS

In a series of twenty-five dogs under identical conditions, one tenth of the estimated lethal dose of a standardized market preparation of the whole leaf of digitalis was given every ten minutes, and in some experiments every seven minutes, until the lethal dose was reached. The preparation used was purchased on the market and was found to be accurately standardized in cat units. One and one-quarter cat units per kilogram was considered as the lethal dose. In the light of our experience we consider this dosage too high. One cat unit per kilogram represents more closely the proper dosage. This preparation will be referred to as whole leaf preparation 1. The series used was large, but we do not consider it to be any too large when important conclusions are to be drawn from animal experiments in which many variations are inherent.

Chart 3 shows the results of such an experiment. The control reading is designated by (*C*), and one tenth of the calculated lethal dose was given directly after the control reading and directly after each of the readings represented by the subsequent numerals. Thus the reading at (*1*) shows the results of the injection of the first fraction, the reading at (*2*) the results of the dose given directly after the readings were taken at (*1*), and so on. In this experiment the coronary

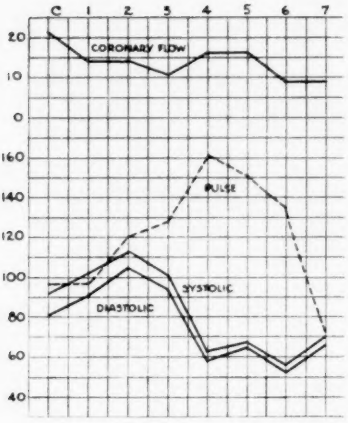

Chart 3.—In this experiment one tenth of the estimated lethal dose of digitalis (whole leaf preparation 1) was given every ten minutes to dog 58. At (*C*) are plotted the coronary flow volume in cubic centimeters per minute, the pulse rate and the systolic and diastolic blood pressure of the last control reading. One tenth of the estimated lethal dose of digitalis was given immediately after (*C*). At (*1*) are shown the coronary flow volume, blood pressure and pulse rate ten minutes later. A second tenth of the estimated lethal dose was given immediately after (*1*), and the results are shown at (*2*), and so on. The volume of coronary flow is seen to decrease after the first dose, in spite of an increase in blood pressure and in pulse rate.

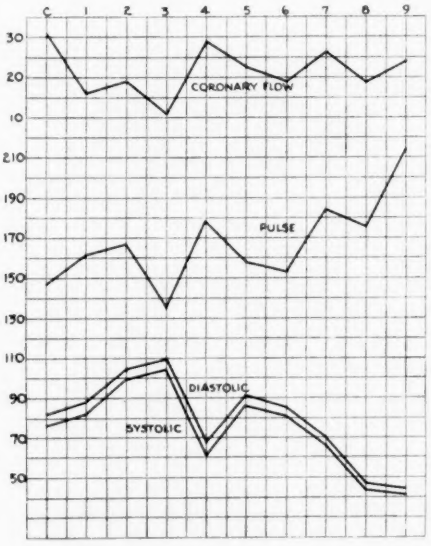

Chart 4.—The results of another experiment (on dog 66) similarly plotted to show the effect of pulse rate on volume of coronary flow, and the decrease in volume of coronary flow with digitalis (whole leaf preparation 1) in spite of an increase in blood pressure and in pulse rate following its administration.

flow is observed to decrease with a rising blood pressure and a rising pulse rate. This chart shows the type of result that we considered to indicate a vasoconstrictor action, and that we shall later classify as "decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate." Chart 4 is shown also in order to illustrate the effect of the pulse rate on the coronary flow volume. The variations in coronary flow in this experiment closely follow the variations in blood pressure, but the fall in blood pressure probably offsets an increase in coronary flow corresponding to the rise in pulse rate. In some cases the coronary flow seems to be more a function of the blood pressure and in other cases more a function of the pulse rate, but usually more or less a resultant of the two.

We have inserted chart 5 to show the type of result that we do not feel justified in accepting as an indication of a vasoconstrictor action, although such an action may have been present. The fall in blood pressure and coronary flow at the second control was caused by a kink in the venous return flow tube. When the digitalis was injected after the fourth control reading, there was a small decrease in coronary flow, but there were also a slight decrease in blood pressure and a marked decrease in pulse rate. It illustrates the type that we have later classified as "decrease in coronary flow accounted for by change in blood pressure or pulse rate." We consider that a vasoconstrictor action could be easily read into this tracing, but it does not admit of proof, and we have not used this or similar results as indicating a vasoconstrictor action.

After from 20 to 30 per cent of the calculated lethal dose has been administered, so many variables appear, owing to the action of digitalis on other cardiac functions that we do not consider that any accurate deductions can be made in regard to the effect of digitalis on the coronary flow. It is probable that most of the digitalis used therapeutically is within these limits.

The results of the experiment with the whole leaf preparation 1 may be summarized as follows:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	12
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	9
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	4

Twelve dogs showed a decrease in coronary flow that could not be accounted for by a fall in blood pressure or pulse rate. In the remainder of the experiments a rise or a fall in the volume of coronary flow followed a rise or a fall in blood pressure or pulse rate. If the

volume of coronary flow is taken as a function of blood pressure alone, the results with whole leaf preparation 1 are as follows (variations in pulse rate disregarded):

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure.	14
Decrease in coronary flow accounted for by fall in blood pressure..	7
Increase in coronary flow accounted for by rise in blood pressure...	3
Increase in coronary flow unaccounted for by rise in blood pressure..	1

According to these results fourteen dogs showed a decrease in coronary flow without a fall in pressure, and in most cases with a rise in pressure. One animal showed an increase in coronary flow without a corresponding increase in pressure, but in the control series similarly considered four dogs showed such an increase.

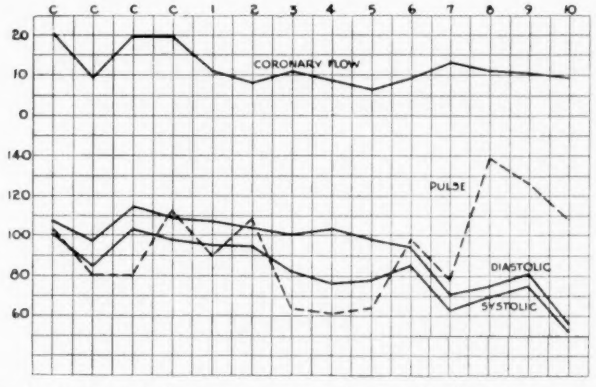

Chart 5.—This graph illustrates the type of result (in dog 60) that is not considered to indicate a decrease in volume of coronary flow due to the action of digitalis (whole leaf preparation 1). The volume of coronary flow decreases, but there is an accompanying fall in blood pressure and in pulse rate. This represents the type of result classified as "decrease in coronary flow accounted for by fall in blood pressure or pulse rate." An accidental interference with the venous return flow occurred at the second control reading.

A composite graph showing the results in the control series and in the series to which whole leaf preparation 1 was given is presented in chart 6. In this the average deviation at each period from the control value is plotted. In spite of a level or slightly increased pulse rate and an increased systolic and diastolic pressure in the animals receiving digitalis, the coronary flow in this series averages decidedly less than in the control series.

To be certain that the results obtained were not due to properties inherent in the preparation used, a second market preparation of the

whole leaf, referred to as whole leaf preparation 2, was used in twelve dogs. The results, which are summarized as follows, are substantially the same as with the first preparation:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	7
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	3
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	2

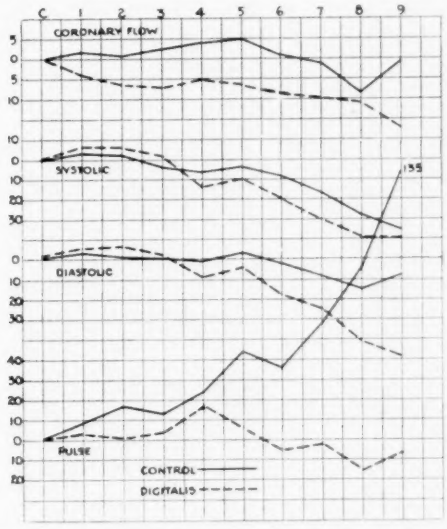

Chart 6.—A composite graph, comparing the results obtained in the series to which whole leaf preparation 1 was administered with the results obtained in the control series receiving no medication. The average deviation from the last control reading at each ten minute interval is plotted from the same base line. The broken lines represent the course followed by the coronary flow and by its determining factors, systolic and diastolic blood pressure and pulse rate, in the series to which digitalis was administered. The solid line represents the course of the coronary flow and its determining factors in the control series. A decreased coronary flow with digitalis is observed, in spite of an increase in the factors that would normally cause an increased flow.

A third digitalis preparation was used, the exact composition of which we do not know. It is a popular and generally used preparation of the whole leaf, which has been subjected to a special process in the course of manufacture. The preparation used in these experiments was a market preparation, standardized to a strength comparable to

the two preceding preparations. The results obtained were quite different from those of the two preceding preparations, as indicated by the following summary:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	1
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	5
Increase in coronary flow accounted for by rise in blood pressure or pulse rate	5

There was evidence of vasoconstriction in only one experiment, and in the others the coronary flow followed normally the changes in blood pressure and pulse rate.

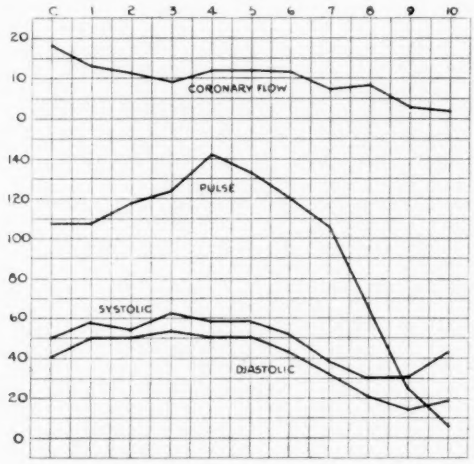

Chart 7.—Result of a single experiment (dog 186) in which whole leaf preparation 2 was used. The coronary flow decreases in spite of an increase in the factors that would normally cause it to increase.

These results were so divergent from those obtained with the other preparations that it was felt that the series should be enlarged, and several months later a second series of eleven dogs was tested, with the following results:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	6
Increase in coronary flow unaccounted for by increase in blood pressure or pulse rate	1

The results of the second series confirmed those obtained in the first series, and would seem to indicate a qualitative difference in the preparations.

We are able to offer no explanation for the difference in the action of this preparation. We have carefully considered the possibility of experimental error.

As will be shown later, no decrease of the volume of coronary flow was observed in vagectomized or atropinized animals. Because of this observation, it was considered possible that this special preparation did not possess a central action. Accordingly the experimental work of Greene and Peeler [12] was repeated by one of us in conjunction with Miss Ruth Trump. In this experiment the head of a turtle was

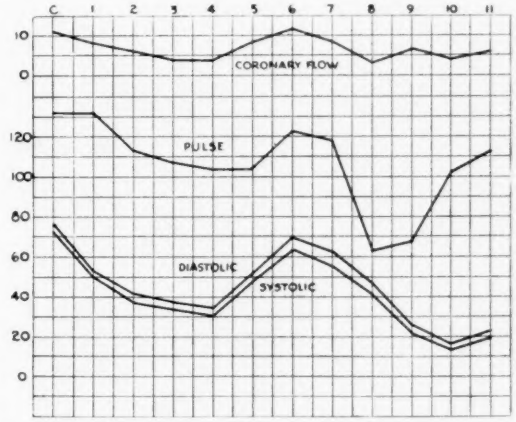

Chart 8.—Results of an experiment on a dog (dog 135) to which whole leaf preparation 1 was administered (one tenth of the estimated lethal dose at ten minute intervals) two days after both cervical vagi had been severed. The coronary flow follows the variations in its determining factors as in the control series.

entirely separated from the body, except for the vagus nerves, and the head was perfused with Ringer's solution, to which was added, after a control period, the drug to be tested. Greene and Peeler showed digitalis under these conditions to have a central effect on rate and conductivity after a short latent period. Whole leaf preparation 1 and special preparation 1 gave results identical with those obtained by Greene, and did not differ from each other.

12. Greene, C. W., and Peeler, J. O.: J. Pharmacol. & Exper. Therap. **7**:591, 1915.

OUABAIN

Standard ouabain obtained from the United States Bureau of Standards through Professor Carlson and made up by Professor Van Dyke gave results similar to those obtained with the first two preparations as follows:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	5
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	2
Increase in coronary flow unaccounted for by increase in blood pressure or pulse rate	1

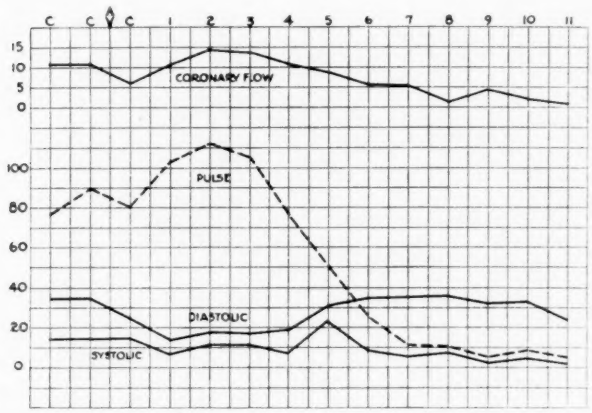

Chart 9.—In this experiment 0.2 mg. of atropine sulphate per kilogram of weight was administered at *A*, and one tenth of the estimated lethal dose of whole leaf preparation 1 was given at ten minute intervals, beginning after the last control period at the third (*C*). There is no evidence of any vasoconstrictor effect of digitalis on the coronary arteries.

Here also evidence of a vasoconstrictor action occurs, although in one of twelve dogs there was an increase in coronary flow without corresponding changes in blood pressure or pulse rate. In a similar series of seven dogs a market preparation of strophanthin was used. The results which are indicated in the following summary were the same as with the standard ouabain, and show evidence of a vasoconstrictor action.

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	3
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4

Digitoxin we found very difficult to obtain at the time when these experiments were done. We used two preparations, one of which was obtained from Germany. From the results obtained by Voegtlein and Macht [2] on arterial strips we should have expected the most marked vasoconstrictor effects from crystallized digitoxin. We actually found much less effect on the coronary flow from this preparation. It is unfortunate that we are not more certain of the quality of our digitoxin. Other effects of digitalis obtained from this preparation were variable. The results with each preparation are as follows:

Digitoxin (American)	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	2
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	2

Digitoxin (German)	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	2
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	5
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	3

In a series of eleven dogs the vagi were cut one or two days before the experiment. There was no evidence of a vasoconstrictor action in these dogs on the administration of whole leaf preparation 1. The results in this series were as follows:

After Vagectomy	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	7
Increase in coronary flow accounted for by rise in blood pressure or pulse rate	4

With the use of atropine, 0.2 mg. per kilogram of weight, before the experiment, similar results were obtained:

After Atropine	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	2
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	8

The results of the experiments on vagectomized and atropinized animals would suggest the possibility at least of an effect on the vagus. Against a purely central effect are the observations with special preparation 1 and the experiments showing that this preparation of the drug has a central effect in the turtle as regards at least rate and conductivity. Against a central action also are the positive results obtained by other authors on artery strips and on the isolated heart. The section of the vagus and the atropine evidently introduce an element not explained in these experiments.

COMMENT

The experiments reported seem to indicate that digitalis does have an effect that decreases the coronary flow. This decrease is observed under conditions of pulse rate and blood pressure that would normally tend to increase the volume of coronary flow.

It is at least possible that there was a decrease in coronary flow in part of the cases in which the blood pressure and the pulse rate fell. However, it is not to be expected that such a vasoconstrictor action would be present in all experimental cases or in all clinical cases. Such an action is not to the biologic advantage of the animal, and it is to be expected that it would be offset by some protective reflex mechanism. Greene [13] and others have stressed the ease with which vasodilator effects may be obtained by nerve stimulation and the difficulty with which vasoconstrictor effects on the coronary arteries are obtained.

Angina pectoris may be assumed to include a large group of cases in which it is probable that vasoconstriction of the coronary arteries occurs as a result of reflexes originating in various sources. Such a reflex vasoconstriction, moreover, is not to the advantage of the patient and does not occur with a normally acting autonomic system, but in persons whose autonomic systems show lowered thresholds and are overlabile. It is in such a group that one would expect a vasoconstrictor action from digitalis to occur on the coronary arteries most readily.

In a large series of clinical cases, as in a large series of experimental animals, digitalis in comparable doses shows a wide divergence of action. The different physiologic effects do not always appear in the normal sequence, or with the same percentage of the lethal dose; or one or another action may not appear at all. The physiologic effect is probably not a simple function, but is conditioned by a great many anatomic and biochemical factors with which we are not as yet familiar.

The coronary flow is also a function of many variable factors, and effect of one isolated factor cannot be predicted. While a vasocon-

13. Greene, C. W.: J. Missouri M. A. **28**:466, 1931.

strictor action cannot be predicted in any case, we feel that there is enough evidence of the presence of such an action to warrant a great deal of caution in the use of digitalis in coronary disease.

CONCLUSION

In a series of experiments on dogs, evidence was elicited indicating that digitalis bodies may exert a vasoconstrictor action on the coronary arteries.

RELATION OF SUGAR TO CHOLESTEROL IN THE BLOOD

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It is known that in diabetes mellitus there is often a distinct increase in the level of both the blood sugar and the plasma cholesterol. The relationship between the fluctuations of these two substances in the blood in diabetes mellitus is not constant, as shown by many observers (Boyd,[1] Joslin, Bloor and Gray,[2] Gray,[3] Rabinowitch,[4] and White and Hunt[5]). McCrudden and Sargent[6] studied the blood cholesterol and sugar in a number of pathologic states and were not able to demonstrate any constant correlation. There are several complicating factors which may arise in the course of diabetes mellitus that may raise either the blood sugar or the plasma cholesterol or both. Thus it is established that severe acidosis and diabetic coma, malnutrition, overnutrition and a high fat intake continued over a long period may bring about a hypercholesterolemia (Bloor[7]), though the blood sugar may be elevated in some of these conditions, but not in others. It becomes obvious that an unvarying direct relationship between dextrose and cholesterol in the blood does not occur because of the numerous, widely differing factors that may influence them.

This research was aided by a grant from the Josiah Macy, Jr., Foundation.

Read before the Association of American Physicians, Atlantic City, N. J., May 4, 1932.

From the Department of Medicine, New York Post-Graduate Medical School and Hospital.

1. Boyd, G. L.: Blood Fat in Diabetic Children, Am. J. Dis. Child. **36**:298 (Aug.) 1928.

2. Joslin, E. P.; Bloor, W. R., and Gray, H.: The Blood Lipoids in Diabetics, J. A. M. A. **69**:375 (Aug. 4) 1917.

3. Gray, H.: Lipoids in 1,000 Diabetic Bloods with Special Regard to Prognosis, Am. J. M. Sc. **168**:35, 1924.

4. Rabinowitch, I. M.: The Cholesterol Content of the Blood Plasma in Diabetes Mellitus, Arch. Int. Med. **43**:363 (March) 1929; The Cholesterol Content of Blood Plasma in Juvenile Diabetes, ibid., p. 372.

5. White, P., and Hunt, H.: Cholesterol of the Blood of Diabetic Children, New England J. Med. **202**:607, 1930.

6. McCrudden, F. H., and Sargent, C. S.: Comparison of the Glucose and Cholesterol Content of Blood, J. Biol. Chem. **33**:387, 1918.

7. Bloor, W. R.: Diet and the Blood Lipoids, J. Biol. Chem. **95**:663, 1932.

It remains to be determined whether the change of the blood sugar level in itself, regardless of acidosis, malnutrition, overnutrition and similar conditions, has any bearing on the concentration of the plasma cholesterol. Such a determination has an obvious and distinct bearing on the clinical interpretation of the cholesterol values, especially in diabetes mellitus.

The present study is an analysis of the concomitant fluctuations in the blood sugar and plasma cholesterol following the ingestion of 100 Gm. of dextrose in ninety-five persons who were normal or gave evidence of either mild diabetes mellitus or renal glycosuria. The test subjects fasted for approximately fourteen hours and were then given 100 Gm. of dextrose in solution by mouth. Synchronous determinations of blood sugar and plasma cholesterol were carried out before the ingestion of dextrose and subsequently at intervals of twenty, forty, sixty and one hundred and twenty minutes. The blood sugar was determined by the Folin-Wu [8] method, and the plasma cholesterol by the Sackett modification of Bloor's method.[9]

The maximal deviation of plasma cholesterol within five hours while the subjects were fasting or during twenty-four hours while they were consuming three meals a day was found to be 7.8 per cent, according to the researches of Bruger and Somach.[10] All variations in the plasma cholesterol in excess of these limits were regarded as fluctuations for which the consumption of the dextrose was responsible. Table 1 details the figures for thirteen cases in which the plasma cholesterol dropped more than 20 per cent, as calculated from the control level, and table 2 presents the data from nine cases in which the plasma cholesterol rose more than 30 per cent. From these tables it is evident that the variations in plasma cholesterol after the ingestion of dextrose may be marked, and that they do not always occur in the same direction.

It is important to check the relation of the type of blood sugar curve, or the dextrose tolerance, to the changes in the plasma cholesterol. If a blood sugar of 120 mg. per hundred cubic centimeters two hours after the taking of dextrose is regarded as normal and a higher blood sugar as indicating a prolonged curve, significant of a diminished dextrose tolerance, it becomes apparent from tables 1 and 2 that, although a rise or a fall of the plasma cholesterol may occur with a normal or a prolonged sugar curve, a drop of cholesterol is more commonly found with the higher glycemia at the end of the two hour period.

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8. Folin, O., and Wu, H.: System of Blood Analysis, J. Biol. Chem. **41**:367, 1920.

9. Sackett, G. E.: Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum, J. Biol. Chem. **64**:203, 1925.

10. Bruger, M., and Somach, I.: The Diurnal Variations of the Cholesterol Content of the Blood, J. Biol. Chem. **97**:23, 1932.

TABLE 1.—*Cases in Which the Plasma Cholesterol Dropped More Than 20 Per Cent After the Ingestion of 100 Gm. of Dextrose* *

Fasting Control		Minutes after Ingestion of Dextrose, 100 Gm.								Duration of Blood Sugar Curve
		20		40		60		120		
Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	
95	173	139	166	86	105	80	127	69	117	Normal
96	183	128	144	145	156	124	166	100	146	Normal
108	204	164	...	230	144	230	237	140	222	Prolonged
94	270	147	214	158	188	158	200	143	188	Prolonged
93	191	142	186	174	167	211	75	150	150	Prolonged
113	189	152	171	190	162	208	136	158	160	Prolonged
114	221	147	194	169	192	188	163	172	168	Prolonged
124	154	179	147	214	158	254	158	254	120	Prolonged
143	222	218	245	...	...	250	175	260	184	Prolonged
203	185	205	179	339	175	285	151	278	139	Prolonged
143	360	165	464	217	272	250	256	300	224	Prolonged
156	194	247	183	291	185	308	175	333	157	Prolonged
227	266	416	240	625	206	500	211	418	245	Prolonged

* The minimal figure for plasma cholesterol is underlined.

* This table gives an indication of the extent to which the plasma cholesterol may fall.

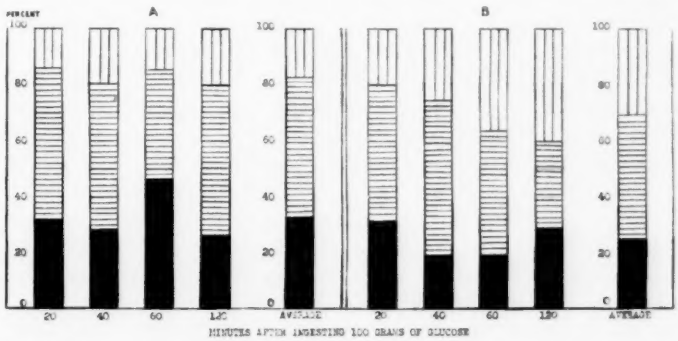
TABLE 2.—*Cases in Which the Plasma Cholesterol Rose More Than 30 Per Cent After the Ingestion of 100 Gm. of Dextrose* *

Fasting Control		Minutes after Ingestion of Dextrose, 100 Gm.								Duration of Blood Sugar Curve
		20		40		60		120		
Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	
79	193	143	258	130	300	111	230	103	202	Normal
100	120	111	160	133	120	125	120	111	109	Normal
93	136	136	136	...	...	167	158	115	188	Normal
91	157	107	176	167	230	176	213	120	200	Normal
77	169	142	222	183	176	183	162	135	175	Prolonged
75	208	120	222	188	286	231	283	150	275	Prolonged
86	193	125	240	...	...	176	300	153	250	Prolonged
125	214	214	260	...	...	259	286	300	278	Prolonged
150	158	211	147	300	167	319	163	375	213	Prolonged

* The maximal figure for plasma cholesterol is underlined.

* This table gives an indication of the height to which the blood cholesterol may rise.

These points are possibly shown more clearly in chart 1. While every one recognizes that 120 mg. per hundred cubic centimeters is a normal blood sugar finding two hours after a test meal of 100 Gm. of dextrose, there are many who believe that the same value in three hours is a sufficient criterion, or that 140 mg. two hours after taking the dextrose is all that is required to establish normal carbohydrate tolerance. Taking these interpretations of what constitutes the criterion for a normal dextrose tolerance into consideration, the ninety-five cases studied have been divided into two groups: those in which the blood sugar at the end of two hours was 140 mg. or less per hundred cubic centimeters (fifty-eight cases) and those in which it was above 140 mg. in two hours (thirty-seven cases). The variations in the plasma cholesterol after ingestion of dextrose are analyzed on this basis in the chart. A study of



Variations in plasma cholesterol after ingestion of dextrose. *A*, blood sugar 140 or less in two hours (fifty-eight cases); *B*, blood sugar above 140 in two hours (thirty-seven cases). The vertical lines indicate a decrease; the horizontal lines, no change, and the solid black, an increase in plasma cholesterol. Controls indicate that the maximal deviation of plasma cholesterol is 7.8 per cent. The height of the columns indicates the percentage of instances in each group.

this chart reveals that after the rise and fall of blood sugar following the ingestion of 100 Gm. of dextrose: 1. The plasma cholesterol may remain constant, rise or fall. 2. The plasma cholesterol remains unchanged in about one half of the cases. 3. Although a diminution or an increase in the plasma cholesterol may occur, whether the dextrose tolerance is normal or impaired, it is evident that the plasma cholesterol is more frequently lowered when the blood sugar is markedly elevated, as is seen in the cases with diminished sugar tolerance sixty and one hundred and twenty minutes after the ingestion of dextrose, and is most often raised when the dextrose tolerance is normal, as is seen in these cases sixty minutes after the ingestion of dextrose.

COMMENT

There is a relation between the level of the blood sugar and that of the plasma cholesterol. As the blood sugar rises after the ingestion of dextrose, the plasma cholesterol may remain constant or increase or diminish appreciably. The factors that bring about these changes in the plasma cholesterol concentration are probably in part compensatory osmotic phenomena, as suggested by the fact that the level of the blood sugar and that of the plasma cholesterol are often inversely proportional. This fact, however, fails to account for the many instances in which the plasma cholesterol is elevated in these observations. The speed and efficiency of the oxidation of dextrose and the storage of dextrose as glycogen in the liver and in other tissues suggest themselves as possible factors that will influence the level of the plasma cholesterol. The results of the present experiments cannot be interpreted as definite evidence in this regard, but they do point to the fact that the metabolism of dextrose has a far-reaching influence on the level of the plasma cholesterol. Furthermore, in diabetes mellitus, although it is evidently true, as has been frequently noted, that the blood sugar and plasma cholesterol do not always vary directly or inversely, there is a relationship that must be considered in the clinical interpretation of these substances in the blood.

Remesow and Matrossowitsch [11] carried out simultaneous sugar and cholesterol determinations of the blood after feeding, and after intravenous injection, of cholesterol in dogs and rabbits. They also obtained similar sugar and cholesterol curves after the injection of epinephrine, insulin and other substances. They find that the dextrose and the cholesterol always rise or fall in the blood in diametrically opposite directions (except after injections of insulin). From this they conclude that cholesterol is invariably converted into carbohydrate when it exists in excess in the blood. This does not agree with the results reported in this paper, since the relation between the blood sugar and plasma cholesterol did not exhibit the constancy reported by Remesow and his collaborator. Furthermore, as studies in the laboratory have shown, the ingestion of dextrose and the subsequent rise in blood sugar are accompanied by variations in the concentration of urea, sodium chloride, the plasma proteins and probably other substances; this would make it appear far-fetched to deny that efforts on the part of the body to maintain an osmotic equilibrium do not play a large part in causing the fluctuations of all of these substances. That cholesterol by some chemical process assumes carbohydrate characteristics is another matter,

11. Remesow, I., and Matrossowitsch, D.: Experimentell-chemische Studien über den Lipoidstoffwechsel. II. Mitteilung. Blutzuckerkurven bei Carnivoren und Herbivoren während der experimentellen Lipämie. III Mitteilung. Über die Veränderungen des Lipoidstoffwechsels, hervorgerufen durch Adrenalin, Insulin und einige Alkaloide, Ztschr. f. d. ges. exper. Med. **77**:67, 1931.

and is a proposal to which one should not agree without more definite proof on the subject than has been submitted hitherto.

CONCLUSIONS

A rise in the dextrose of the blood, brought about by the ingestion of 100 Gm. of dextrose, is accompanied by variations in the concentration of the plasma cholesterol. The plasma cholesterol may remain constant or may rise or fall appreciably. Compensatory osmotic phenomena may account for some of these fluctuations but not for all of them.

CONGESTIVE HEART FAILURE

XVII. THE MECHANISM OF DYSPNEA ON EXERTION

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To the fundamental studies of Sir James MacKenzie we are indebted for the concept that in cardiac disease the patient's response to effort constitutes the best index to prognosis and the most accurate guide to therapy. Although most clinicians would agree that the patient's dyspnea, that is, his subjective respiratory distress, is the most important clinical phenomenon in cardiac disease, an adequate explanation of the mechanism of this symptom has yet to be offered.

The generally accepted idea of respiratory control involves the assumption that any muscular effort that is sufficiently severe to increase the ventilation is necessarily associated with shifts toward acidity in the blood or in the respiratory center itself. According to Haldane,[1] Winterstein [2] and numerous other authors, the activity of the respiratory center is dependent almost entirely on the hydrogen ion concentration of the arterial blood. The recent studies of Gesell [3] have demonstrated the importance of the blood flow through the respiratory center in the regulation of breathing and have led to the more or less general recognition of the fact that increased acidity of either the arterial or the venous blood may be responsible for greater ventilation. According to these ideas, one has to assume that when a normal person performs muscular exercise, his breathing increases either because of a pouring of acid into the blood stream or because of a lessened circulation to the brain. In the former case, alterations in the composition of the blood passing to the brain are postulated; in the latter case, changes in the state of the blood passing from the brain must be assumed.

From the Department of Medicine, Vanderbilt University.

1. Haldane, J. S.: Respiration, New Haven, Conn., Yale University Press, 1922, p. 185.

2. Winterstein, H.: Die Regulierung der Atmung durch das Blut, Arch. f. d. ges. Physiol. **138**:167, 1911.

3. Gesell, R.: The Chemical Regulation of Respiration, Physiol. Rev. **5**:551, 1925.

DYSPNEA

The application of these concepts to the problem of dyspnea produced by exertion in patients with disease of the heart has led to a widely accepted belief that the patient with an abnormal heart suffers during exertion from either actual or relative diminution in the output of his heart. That such patients exhibit, after a given amount of exertion, greater ventilation than do normal persons has generally been attributed to a diminution in cerebral blood flow and a consequently greater shift toward acidity in the respiratory center. As examples of this point of view, one may quote Means,[4] who wrote:

> The fundamental fault responsible for cardiac dyspnea is obviously to be found not in the nature of the blood but in the rate at which it is pumped; in the heart itself. . . . Into the varieties of heart disease we need not go. The factors leading to dyspnea are common to all. The important point is that the heart, either because of increased work, fatigue or degeneration, is unable to maintain an adequate rate of blood-flow. . . . In brief, then, we may assume that in cardiac disease there may, through slow blood flow, be delay both in getting oxygen in and carbon dioxide out.

Meakins and Davies[5] said:

> We are pursuing further work on this question but we would suggest that cardiac failure of this character is due to an incomplete ventricular systole as a consequence of which the circulation rate is greatly and progressively diminished. . . . Therefore, a general cellular oxygen want and cellular carbon dioxide acidosis would develop with all the typical symptoms of dyspnea, weakness, exhaustion, precordial discomfort and even loss of consciousness.

It may be noted, however, that no one has yet reported data obtained from analysis of the blood at rest and during mild exertion which indicate that the alterations in the composition of the blood postulated in these views are actually present.

On the contrary, in a recent study made by Cullen, Harrison, Calhoun, Wilkins and Tims,[6] the following results were obtained:

> 1. Neither during nor after exercise were significant alterations observed in the hydrogen ion concentration, carbon dioxide content, carbon dioxide pressure or oxygen content of *arterial* blood. The exercise was mild but sufficient to cause a well marked increase in ventilation and to cause slight or moderate dyspnea in persons with cardiac disease.
>
> 2. Likewise, muscular exertion produced no changes in the composition of the blood from the *internal jugular vein.*

4. Means, J. H.: Dyspnea, Medicine **3**:388, 1924.

5. Meakins, J. C., and Davies, H. W.: Respiratory Function in Disease, Edinburgh, Oliver & Boyd, 1925, p. 328.

6. Cullen, G. E.; Harrison, T. R.; Calhoun, J. A.; Wilkins, W. E., and Tims, M. M.: Studies in Congestive Heart Failure: XIII. The Relation of Dyspnea of Exertion to Oxygen, Carbon Dioxide and Hydrogen Ion Concentration of the Blood, J. Clin. Investigation **16**:807 (Oct.) 1931.

3. Ammonium chloride caused a relatively great decrease in p_H and in carbon dioxide content, but caused only a slight increase in ventilation, whereas mild muscular activity caused a relatively striking increase in ventilation and no significant change in blood acidity or gases.

Chart 1, showing some of these points, is illustrative of but one of a fairly large series of observations in which similar results were encountered.

This work demonstrated that the increase in ventilation which occurs in the performance of mild exercise, and which ordinarily suffices to produce discomfort in persons with cardiac disease, is not due to changes in the composition of the blood or to diminution in the blood supply to the respiratory center. The cause of dyspnea on mild exertion had to be sought elsewhere.

The valuable observations of Peabody and his co-workers [7] have indicated the great importance of the vital capacity as a measure of the tendency toward dyspnea. With these studies as a basis, Harrison, Turley, Jones and Calhoun [8] attempted to arrive at a somewhat more quantitative measurement of this symptom. The results indicated that the ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ constitutes a fairly certain numerical guide. In other words, dyspnea tends to result from any process that diminishes the vital capacity, or from any cause that increases ventilation.

Diminished Vital Capacity as Cause of Dyspnea.—In persons with cardiac disease the vital capacity is usually lower than in normal persons. This diminution tends to cause dyspnea in two different ways:

(*a*) Per se it lowers the respiratory reserve and hence means that for any given level of ventilation dyspnea is more likely to occur.

7. Peabody, F. W.: Clinical Studies on the Respiration: I. The Effect of Carbon Dioxid in the Inspired Air on Patients with Cardiac Disease, Arch. Int. Med. **16**:846 (Nov.) 1915; II. The Acidosis of Chronic Nephritis, ibid. **16**:955 (Dec.) 1915; III. A Mechanical Factor in the Production of Dyspnea in Patients with Cardiac Disease, ibid. **20**:433 (Sept.) 1917. Peabody, F. W., and Wentworth, J. A.: IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, ibid. **20**:443 (Sept.) 1917. Peabody, F. W.; Wentworth, J. A., and Barker, B. I.: V. The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, ibid. **20**:468 (Sept.) 1917. West, H. F.: VI. A Comparison of Various Normal Standards for the Normal Vital Capacity of the Lungs, ibid. **25**:306 (March) 1920. Peabody, F. W., and Sturgis, C. C.: VII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, ibid. **28**:501 (Nov.) 1921. Sturgis, C. C.; Peabody, F. W.; Hall, F. C., and Fremont-Smith, F.: VIII. The Relation of Dyspnea to the Maximum Minute-Volume of Pulmonary Ventilation, ibid. **29**:236 (Feb.) 1922. Peabody, F. W., and Sturgis, C. C.: IX. The Effect of Exercise on the Metabolism, Heart Rate and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease, ibid. **29**:277 (March) 1922.

8. Harrison, T. R.; Turley, F. C.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure: X. The Measurement of Ventilation as a Test of Cardiac Function, Arch. Int. Med. **48**:377 (Sept.) 1931.

(*b*) A decrease in vital capacity also tends to cause a reflex increase in breathing. This was shown by Harrison, Cullen, Calhoun, Wilkins and Pilcher.[9] Their findings may be briefly summarized as follows:

1. Experimental diminution of the vital capacity of dogs by any one of several methods resulted in an increased rate and volume of breathing, provided the vagus nerves were intact. After these nerves had been cut, the same procedures were not ordinarily accompanied by changes in respiration.

2. During these procedures analyses were made of arterial blood and of venous blood from the brain. A slight or moderate reduction of vital capacity was not accompanied by significant changes in the acid-base condition or gases of the blood, but was associated with increased ventilation in animals with intact vagi. A more marked decrease in vital capacity caused deficient aeration of the blood and resulted in increased ventilation even when the vagus nerves had been cut.

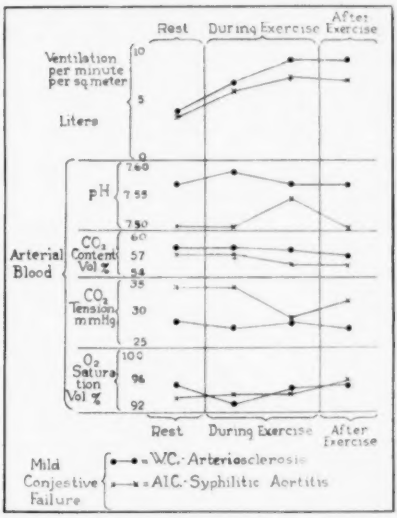

Chart 1.—The chart is constructed from the data of Cullen, Harrison, Calhoun, Wilkins and Tims. The values for p_H and carbon dioxide represent determinations on serum, whereas the analyses for oxygen content were done on whole blood. In both patients the ventilation during and after exercise was considerably greater than at rest. The arterial blood did not become more acid and its carbon dioxide tension did not increase. Likewise significant alteration in the oxygen and carbon dioxide content did not occur.

3. No evidence of consistent alteration in cerebral blood flow was found in the experiments.

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9. Harrison, T. R.; Cullen, G. E.; Calhoun, J. A.; Wilkins, W. E., and Pilcher, C.: Studies in Congestive Heart Failure: XV. Reflex Versus Chemical Factors in the Production of Rapid Breathing, J. Clin. Investigation **11**:133, 1932.

This study indicated clearly that diminished vital capacity causes a reflex increase in ventilation, the afferent path being through the vagus nerves. The average values for the vital capacity of the subjects portrayed in charts 2 and 3 were 2.3 liters per square meter for the normal persons and 1.6 liters per square meter for the patients. It is therefore evident that the increase in rate and volume of respiration which was observed at rest in these patients can be attributed to the reflex effects of a diminished vital capacity.

Since the effects of relatively slight diminutions in vital capacity were so striking, it was thought at first that the greater ventilation during mild exertion might be due to a diminution in vital capacity brought

TABLE 1.—*The Effect of Muscular Exertion on the Vital Capacity*

	Vital Capacity, Liters	
Normal Subjects	Rest	Immediately After Exercise
W. E. W.	4.35	4.20
T. B.	3.05	3.05
T. R. H.	4.20	4.35
H. W.	4.45	4.45
W. G. H.	4.40	4.30
M. M. T.	3.55	3.55
B. W.	3.70	3.55
H. F.	3.50	3.70
Persons with Cardiac Disease		
L. C.	3.05	2.80
C. C.	2.45	2.65
E. G.	2.75	2.60
W. C.	2.95	2.90
M. M.	3.15	3.05
L. F.	2.95	2.95
L. Cl.	1.95	1.95

about by muscular activity. Actual observations concerning this point showed that this was not the case (table 1).

These observations seem to clarify the rôle of diminished vital capacity in the production of dyspnea on exertion. Even at rest the vital capacity is decreased and this predisposes to dyspnea, but, since the vital capacity does not undergo further diminution during exercise, it is evident that the cause of the actual appearance of dyspnea during exertion must be sought in changes in the ventilation.

Increased Ventilation as a Cause of Dyspnea.—The ventilation in patients with cardiac disease is greater than normal at rest, during exertion and after exertion. This is illustrated in chart 2, in which are plotted the average results of the measurements of ventilation in a group of nine persons with cardiac disease as compared with four normal persons, the values being expressed in terms of ventilation per square meter. The curves of the respiratory rate are similar in the two groups except that the patients with cardiac disease breathed faster throughout the

observations. The ventilation curves show that the respiratory minute volume of the patients was also greater during each minute. This was not the only deviation from the normal, for (chart 3) the degree of increase in ventilation was, after the first minute of the exercise, greater in the patients than in the controls. Furthermore, the percentage increase in ventilation after the exercise (chart 3, upper part) was also greater in the patients, and the return to the resting level of ventilation was slower in the patients than in the controls. The actual average figures for the total excess ventilation were in the normal subjects 11.2 liters or 2.9 times the resting value and in the patients 15.7 liters or 3.4 times the resting value. From these findings it is clear that an adequate explanation for these changes in ventilation—and consequently a satis-

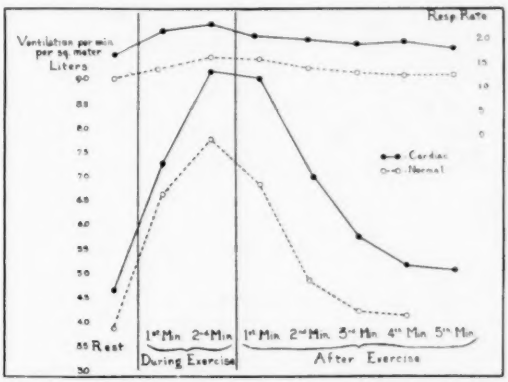

Chart 2.—The two upper curves represent the respiratory rates of normal subjects and patients with cardiac disease, respectively. Throughout the observations the latter persons breathed faster, and after exercise their respiratory rates remained elevated somewhat longer. The two lower curves represent ventilation. The patients had greater ventilation at rest, a greater degree of increase in ventilation during exercise and a slower return to normal after the exercise than was the case in the normal subjects. In both groups the ventilation was greater during the second than during the first minute of the work.

factory understanding of the mechanism of dyspnea—involves the answer to two questions:

1. Why is mild exertion (of degree insufficient to produce alteration in the composition of the blood) associated with an increase in ventilation both in patients with cardiac disease and in normal persons?

2. Why does exercise cause an increase in ventilation which is greater (actually and relatively) in patients with cardiac disease than in normal subjects?

CLINICAL AND EXPERIMENTAL DATA

We have already pointed out that studies of the hydrogen ion concentration and of the gases of the blood failed to reveal changes during or after exercise that was mild but that caused increased breathing and dyspnea in patients with cardiac disease. Therefore it seemed evident that there were two possible causes of the increase in ventilation: (*a*) It was due to some chemical stimulus other than alterations in the blood gases or the hydrogen ion concentration, or (*b*) the effect was of "nervous" origin.

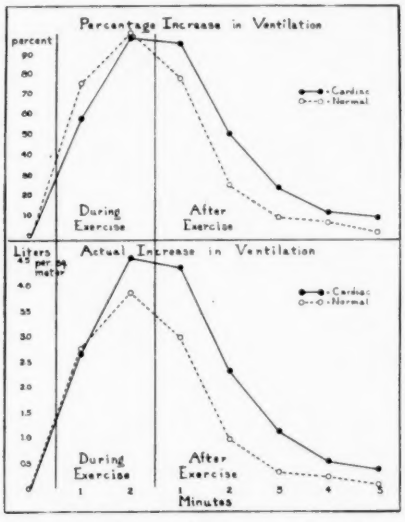

Chart 3.—In the lower portion are depicted the actual increases in ventilation. During the first minute of the exertion the two groups had about the same degree of increase, but in the subsequent minutes the patients had a greater increase. It is noteworthy that the ventilation of the patients was still above the resting value five minutes after the exercise. In the upper portion the percentage increase in ventilation is shown. During the exercise the control subjects had a relatively greater (though actually less) increase in ventilation, whereas after the exercise the ventilation of the patients was not only actually but relatively increased to a greater degree.

The first of these hypotheses seemed to us unlikely for a number of reasons, but it was felt that it should be put to experimental test.

A. Evidence that the Increased Ventilation Produced in Man by Mild Muscular Exercise Is Not of Chemical Origin.—As subjects, three patients with cardiac disease were used. In some instances the expired air was collected in a Tissot spirometer and the respirations were

counted, while in others a graphic record of the breathing was obtained with a Benedict spirometer and the ventilation was calculated from the tracing.

1. The Effect of Active Movements of the Extremities on the Ventilation: The movements consisted of rapidly opening and closing the hands or of rotating the feet. Care was taken, for reasons given

TABLE 2.—*The Effect of Muscular Movements on the Ventilation of Patients with Cardiac Disease*

Subject	Diagnosis	Ventilation per Minute, Liters		
		Before	During	After
A. The Effect of Active Movements with the Circulation Intact				
S. J.	Emphysema, chronic bronchitis, mild congestive failure..	7.78	9.05	8.54
		8.32	9.36	8.73
R. J.	Hypertension, mild congestive failure.....	6.66	9.16	6.86
W. C.	Hypertension, mild congestive failure.....	7.90	10.80	9.98
	Average.....	7.67	9.59	8.53
B. The Effect of Active Movements with the Circulation Impeded by Pressure				
S. J.	Emphysema, chronic bronchitis, mild congestive failure..	8.26	9.70	8.70
		8.32	10.60	9.15
R. J.	Hypertension, mild congestive failure.....	8.12	8.74	7.28
W. C.	Hypertension, mild congestive failure.....	7.48	10.80	10.38
	Average.....	8.04	9.96	8.88
C. The Effect of Passive Movements with the Circulation Intact				
S. J.	Emphysema, chronic bronchitis, mild congestive failure..	9.25	12.45	10.46
		8.32	10.20	7.90
R. J.	Hypertension, mild congestive failure.....	6.45	7.70	6.87
W. C.	Hypertension, mild congestive failure.....	....	....	....
	Average.....	8.01	10.12	8.41
D. The Effect of Passive Movements with the Circulation Impeded by Pressure				
S. J.	Emphysema, chronic bronchitis, mild congestive failure..	9.00	10.70	9.54
		8.73	11.23	8.73
R. J.	Hypertension, mild congestive failure.....	6.24	8.12	6.45
W. C.	Hypertension, mild congestive failure.....	....	....	....
	Average.....	7.99	10.01	8.28
E. The Effect of Releasing the Pressure and Restoring the Circulation after Muscular Movements				
S. J.	Emphysema, chronic bronchitis, mild congestive failure..	8.52		9.98
		8.11		9.36
R. J.	Hypertension, mild congestive failure.....	6.87		7.70
		6.66		6.87
W. C.	Hypertension, mild congestive failure.....	8.92		9.56
	Average.....	7.82		8.69

later, to insure that the muscles above the elbows and knees did not participate in the movement.

As shown in part A of table 2, the ventilation of each of the subjects was greater during the movements than it was before or after them. The different subjects, though showing similar qualitative affects, varied in the degree of response. This was probably dependent on the fact that some of them made stronger movements than did the others. None

of the subjects knew what was expected of him and hence it is not conceivable that psychic influence could have been responsible for the change in breathing.

2. The Effect of Active Movements of the Extremities on the Ventilation When the Circulation to and from the Moving Muscles Is Blocked: In order to attempt to determine whether the increase in ventilation was or was not due to chemical alterations in the blood

TABLE 3.—*The Effect of Muscular Movements on the Ventilation of Normal Men*

Subject	Portion of Body Moved	Respiratory Rate			Ventilation per Minute, Liters		
		Before	During	After	Before	During	After
A. The Effect of Active Movements with the Circulation Intact							
W. E. W.	Hands and feet	15	23	17	7.70	12.06	8.53
T. R. H.	Hands and feet	8	22	8	6.85	18.40	7.03
G. E. C.	Feet	15	16	15	7.24	8.73	8.10
T. B.	Hands	14	18	14	7.56	12.30	8.70
B. The Effect of Active Movement with the Circulation Impeded by Pressure							
W. E. W.	Hands and feet	16	27	17	7.70	13.20	8.32
T. R. H.	Hands and feet	8	18	9	6.49	15.32	5.95
G. E. C.	Feet	17	18	16	8.32	8.52	7.70
T. B.	Hands	13	20	13	8.36	14.10	8.37
C. The Effect of Passive Movements with the Circulation Intact							
W. E. W.	Hands and feet	..	..	..	....	.....	....
T. R. H.	Hands and feet	..	..	..	....	.....	....
G. E. C.	Feet	16	19	18	7.70	8.94	7.70
T. B.	Hands	14	17	14	8.71	11.30	8.71
D. The Effect of Passive Movements with the Circulation Impeded by Pressure							
W. E. W.	Hands and feet	..	..	..	....	.....	....
T. R. H.	Hands and feet	..	..	..	....	.....	....
G. E. C.	Feet	19	17	14	8.11	8.74	7.28
T. B.	Hands	14	18	15	8.71	11.95	9.02
E. The Effect of Releasing the Pressure and Restoring the Circulation after Muscular Movements							
W. E. W.	Hands and feet	16		16	8.11		9.78
T. R. H.	Hands and feet	8		7	5.76		6.66
G. E. C.	Feet	16		14	7.28		7.28
T. B.	Hands	15		14	8.37		8.12

returning to the general circulation from the exercising muscles and affecting the respiratory center, the observations were repeated but with blood pressure cuffs inflated to 200 mm. placed around the proximal portions of the extremities. An effort was made to be certain that no movement took place in the muscles proximal to the cuff. The findings are shown in table 2, part B, and it can be seen that under these conditions the ventilation increased during the exercise to about the same degree as was the case when there was no impediment to the circulation.

In order to determine whether this rather surprising result was a representative physiologic response or whether it was in some way

related to the presence of cardiac disease in the subject, the observations were repeated on normal men. Here again the breathing increased, when muscular movements were performed, regardless of whether or not the circulation to the moving parts was intact (table 3, parts A and B).

In charts 4 and 5 are shown respiratory records from a normal subject and from a patient with cardiac disease, respectively. In each instance the respiratory rate and ventilation increased during muscular movements whether or not the circulation was intact.

These observations admitted of two alternative interpretations: Either, (*a*) since the circulation through the bone was not blocked, the increase in ventilation was due to respiratory stimulation by some chemical substance reaching the general blood stream by means of the veins draining the bone, or (*b*) the increase in ventilation was of "nervous" and not of "chemical" origin.

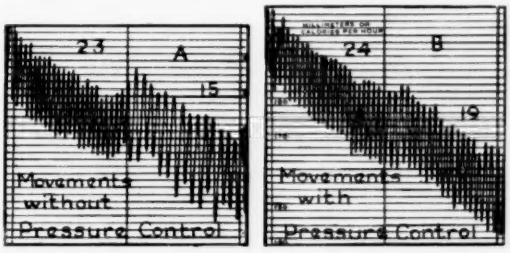

Chart 4.—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. Movements of the hands caused an increase in the respiratory rate and in ventilation whether or not the circulation was intact.

In a later portion of this paper it will be shown that the first hypothesis is untenable because muscular movements in dogs cause an increase in ventilation even when the moving extremity is entirely amputated except for its nerve and vessels and when the latter are clamped (see table 4 and chart 14). Hence, the second assumption would seem to be the correct one.

B. Evidence that the Increased Ventilation Produced in Man by Mild Muscular Movements Is of Reflex Origin.—If the increase in ventilation in the type of exercise investigated is not due to alteration in the composition of the blood, it is presumably of nervous origin. If this is assumed to be true, two alternate explanations present themselves. Either (*a*) the phenomenon is of cortical origin, i. e., is due to an "overflowing" to the respiratory center of impulses from the motor areas of the cerebrum to the voluntary contracting muscles, or (*b*) it is a reflex from some part of the moving extremity to the respiratory center.

Krogh and Lindhard [10] found that the ventilation increases abruptly with the beginning of exercise and that this effect comes on too soon to be due to alterations in the hydrogen ion concentration of the blood. Because of the fact that the ventilation increased when the subject remained at rest but was led to expect that work would be performed, these authors concluded that the increase in ventilation was due to irradiation of impulses from the higher centers to the respiratory center

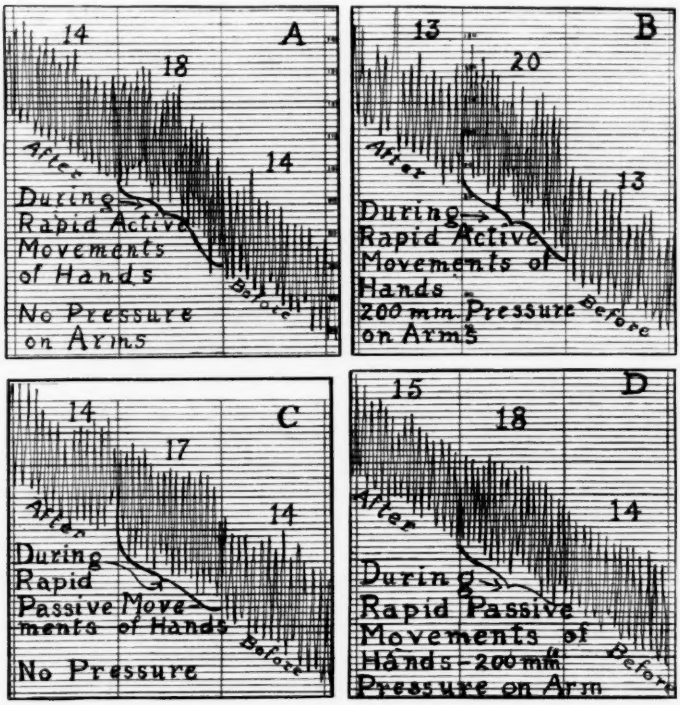

Chart 5.—The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

rather than to reflexes. In a later study Krogh and Lindhard [11] made observations concerning the effect on the respiration of muscular work that was not voluntary but was induced by electrical stimulation of the muscles. They concluded that in this type of work the immediate

10. Krogh, A., and Lindhard, J.: The Regulation of Respiration and Circulation During the Initial Stages of Muscular Work, J. Physiol. **47**:112, 1913.

11. Krogh, A., and Lindhard, J.: A Comparison Between Voluntary and Electrically Induced Muscular Work in Man, J. Physiol. **51**:182, 1917.

increase in respiration was of reflex origin, but their observations did not allow them to differentiate clearly between the respiratory effects due to the movements and those due to the electrical current.

1. The Effect of Passive Movements of the Extremities on the Respiration When the Circulation to and from the Moving Muscles Is Intact: In order to test this matter further we have observed the effect of passive movements. The subject was instructed to make no voluntary movements and to relax the extremities which were to be moved. In order to distract his attention he was instructed to read throughout the course of the observations. The operators of this experiment moved the extremities rapidly either by alternately flexing and extending the hands or by rotating the feet. The results are shown in tables 2 and 3, part C and in chart 5; it can be seen that each subject showed an increase in ventilation during the passive movements, the degree of increase being about the same as that found with active movements.

2. The Effect of Passive Movements of the Extremities on the Ventilation When the Circulation to and from the Moving Muscles Is Blocked: In order to be certain that the increase in ventilation occurring during passive movements was not due to some alteration in the blood, the observations were repeated with pressure around the proximal portions of the extremities. As can be seen in tables 2 and 3, part D, the respiratory response was similar to that occurring with passive movements when the circulation was intact.

3. The Effect on the Ventilation of Reestablishing the Circulation Through Muscles Which Had Been Exercised While the Circulation to and from Them Was Blocked: In order to obtain further information concerning the relative importance of chemical and nervous effects on respiration, the ventilation was observed following the release of the cuffs. These had been in place for seven minutes: for three minutes before, for one minute during and for three minutes after exercise. The results are seen in tables 2 and 3, part E. In most of the subjects a slight increase in ventilation occurred when the circulation was reestablished. This effect was much less than that obtained by muscular movements. In two persons no increase in ventilation occurred when the cuffs were released.

C. Proof That the Increase in Ventilation Produced in Dogs by Mild Muscular Movements Is of Reflex Origin.—One might be tempted to believe that the observations which have been reported constituted final proof that, in the type of muscular movements under consideration, the increase in ventilation was due to reflex rather than to chemical factors.

We do not believe that such an assumption is justifiable from the data that have been presented, for the following reasons:

1. The possibility remains that some blood from the exercising muscles returned to the general circulation through the bones, and it might

be argued that this blood was responsible for the changes observed in ventilation in those experiments in which the venous return was obstructed by compression of the proximal portions of the moving extremities.

2. It is possible that imperceptible contractions of muscles proximal to the cuffs may have caused alterations in the composition of the blood.

In order to meet these objections, experiments were performed on dogs. The animals were given barbital, approximately 0.3 Gm. per kilogram of body weight, intravenously, about one hour before the beginning of the experiment. Tracheotomy was done. In some instances respiration was recorded by having the animal rebreathe oxygen from a Benedict spirometer. When it was desired to obtain accurate measurements of the ventilation a different method was used, the expired air being passed through a two-way tap from which it could be collected in either one of two Benedict spirometers, one of which could be emptied while the animal was breathing into the second.

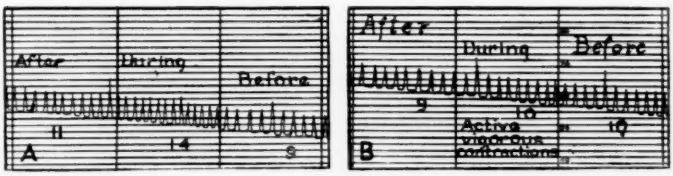

Chart 6.—*A*, passive movement of right leg with intact nerve. *B*, stimulation of peripheral end of left cut sciatic nerve. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

Passive movements were performed at the rate of about three hundred per minute, an effort being made to avoid moving any part of the dog's body other than the extremity in question. This was not entirely possible (except in the final group of experiments in which the hip joint was amputated), as it was often necessary to "shake" vigorously in order to elicit any respiratory response at all. It was found that different animals varied markedly in their response, the degree of increase in ventilation being less in those animals which were most deeply anesthetized and particularly so when, in addition, they were in a state of severe shock.

1. The Effect of Movements of the Hind Leg with and Without the Cutting of the Sciatic Nerve: Such an experiment is shown in chart 6. Passive movements of the intact right leg caused an increase in respiration. Active movements in the opposite leg—induced by stimulation of the peripheral end of the cut sciatic nerve—had no such effect. However,

this experiment was not convincing because the mass of muscle moving was less in the latter than in the former instance.

2. The Effect of a Tourniquet Around the Leg on the Respiratory Response to Passive Movements: In chart 7 it is shown that the ventilation was increased by passive movements whether or not the vessels were compressed by a tourniquet. The tourniquet was tightly drawn and probably obstructed most of the circulation except that through the bone. However, since the latter circulation was not occluded, the experiment must be considered inconclusive.

3. The Effect of Cutting the Spinal Cord on the Respiratory Response to Passive Movements: The animal portrayed in chart 8 showed a definite, although slight, response to movements of the hind-leg and of the fore-leg when the spinal cord was intact (in the charts,

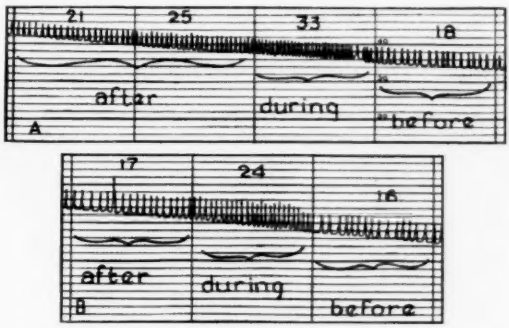

Chart 7.—*A*, passive movements of intact leg. *B*, passive movements of leg-tight tourniquet around all parts of leg except sciatic nerve. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

for the sake of convenience in labeling, "leg" refers to the hind-leg and "arm" to the fore-leg). After chordotomy at the level of the sixth dorsal vertebra, the respiration was not affected by passive movements of the hind-leg but became accelerated when the fore-leg was moved.

In another animal (chart 9) more striking results were obtained. When the spinal cord was intact, well marked effects were obtained by moving the tail, the hind-leg, the fore-leg and the head, in the order of increasing response. It was noted that the mass of muscle being moved was least when the tail was moved, more with the hind-leg, still more with the arm and most with the head. After the spinal cord had been cut at the fourth dorsal level, passive movements of the fore-leg and of the head gave the same response as before, whereas movements of the hind-leg and of the tail were without effect.

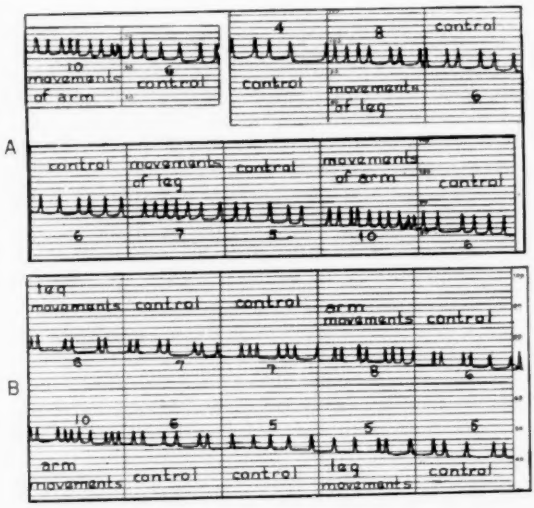

Chart 8.—*A*, spinal cord intact. *B*, spinal cord cut at sixth dorsal level. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

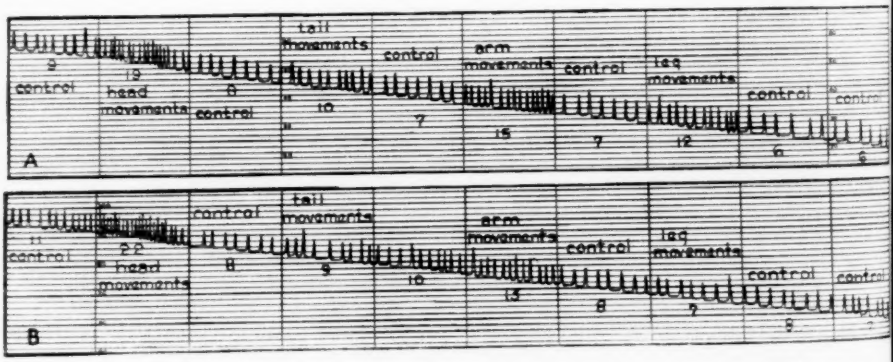

Chart 9.—*A*, spinal cord intact. *B*, spinal cord cut at fourth dorsal level. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

In chart 10, however, is a tracing from an animal that exhibited a well marked increase in ventilation on moving the hind-leg after the spinal cord was cut. This result, which was obtained several times, was surprising. It may be noted that the spinal cord was cut at a lower point in this animal than in the previous ones, although the level was above that of the sensory fibers from the legs. Consequently, it was decided to cut the cord at two different levels and note the effect. Such an experiment is shown in chart 11. When the cord was intact, the usual increase in ventilation resulted from moving the various portions. Chordotomy at the level of the eighth dorsal vertebra did not change the response. However, after the cord had been cut at the third dorsal vertebra the respiration did not increase when the tail or hind-leg was moved, but did increase when the head or fore-leg was moved.

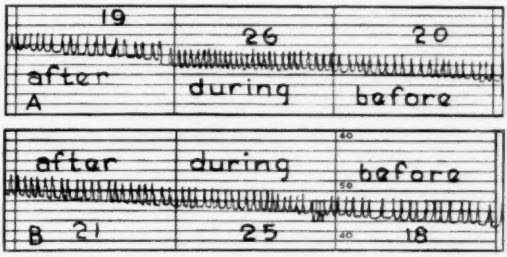

Chart 10.—Passive movements of leg with spinal cord cut at ninth dorsal level. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

If one assumed that one was dealing with a reflex, it was believed that these rather curious findings could have one of three possible explanations:

(*a*) The afferent path might be through the sympathetic chain.

(*b*) The greater degree of shock after chordotomy at the higher levels might abolish the effects from the caudal parts of the body without abolishing those from the cephalic portions.

(*c*) The slight movements in the muscles of the abdomen and buttocks when the hind-leg was moved might have been responsible for the effect when the cord was cut at a level lower than the sites of entry of the sensory nerves from these muscles, whereas, with the higher chordotomies, impulses from these areas as well as those from the tail and hind-leg would have been blocked.

In order to determine which of these explanations was correct, further observations were made.

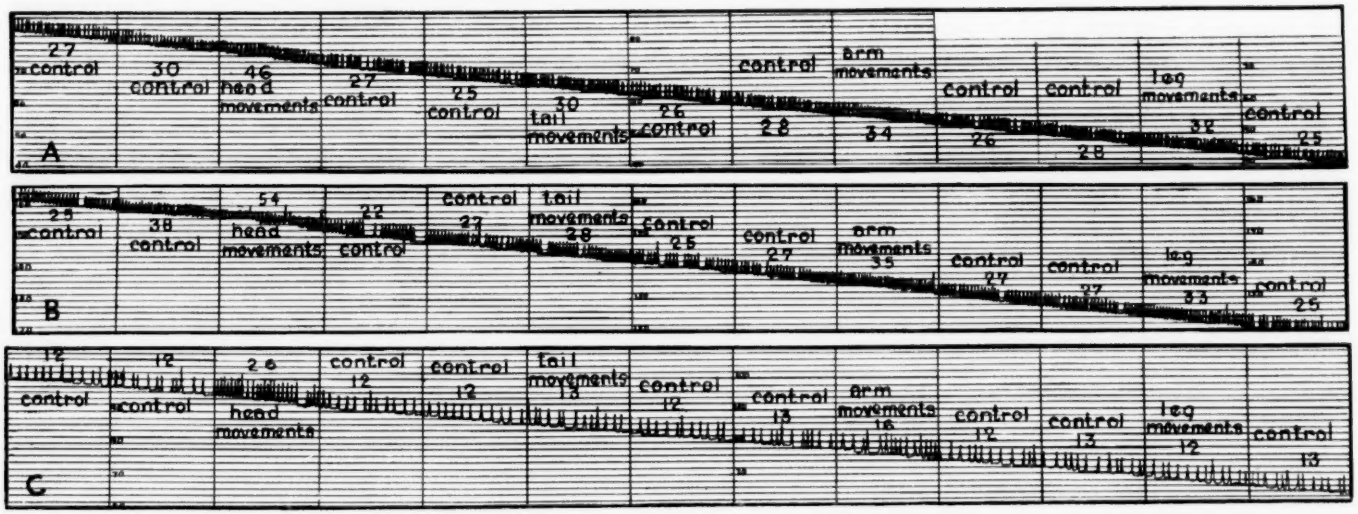

Chart 11.—*A*, spinal cord intact. *B*, spinal cord cut at eighth dorsal level. *C*, spinal cord cut at third dorsal level. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

4. The Effect of Unilateral Sympathectomy on the Respiratory Response to Passive Movements: Chart 12 is the record from a dog in which the left sympathetic trunk had been cut high in the abdomen. Moving the two hind-legs had practically identical effects on the breathing. It is therefore evident that the pathway for the (hypothetic) reflex under discussion does not lie through the sympathetics.

5. The Effect of Cutting the Posterior Spinal Roots on the Respiratory Response to Passive Movements: The animal portrayed in chart

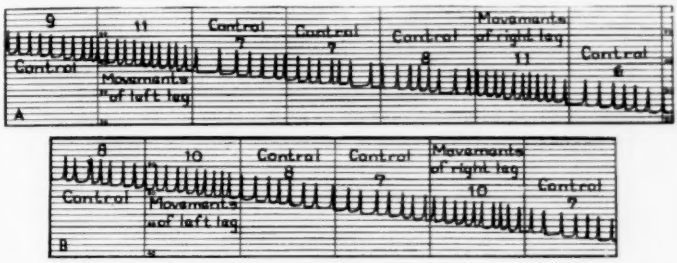

Chart 12.—Left abdominal sympathetic cut. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

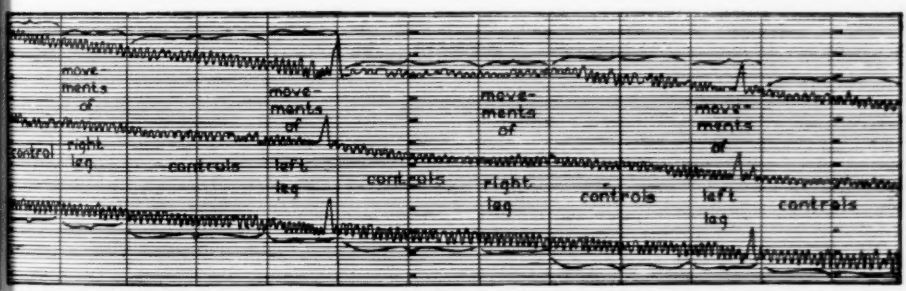

Chart 13.—Right posterior roots cut. The curve runs from right to left. The distance between the vertical lines represents one minute.

13 had been operated on about a year previously, at which time the lower dorsal, the lumbar and the sacral posterior roots on the right side had been sectioned. It was desired to save the animal, and consequently morphine was used instead of barbital. The breathing was rather irregular, and a significant, consistent increase in respiratory rate was not obtained by moving either hind-leg. The qualitative response, however, was decidedly different, as a deep sigh took place whenever the leg with an intact nerve supply was moved, whereas this did not occur when

the leg that had been deprived of sensation was moved. Again the results speak for some kind of reflex effect, but they are rather inconclusive.

6. The Respiratory Response to Passive Movements of Legs Completely Amputated Except for the Femoral Vessels and the Sciatic Nerve: To the experiments on both men and dogs reported up to this point, two objections can be raised. In the first place, since the bones were intact there is the possibility that the results were influenced by blood returning from the moving extremity. In the second place, it seems likely that the respiration was affected by motions of the muscles of the buttocks and of the abdomen. Although the data that have been presented point toward such an effect being reflex, it might conceivably have been chemical, as it was not possible when dealing with intact extremities to move them without causing some movements higher up, and in no case was the venous return obstructed from these more proximal muscles.

In order to meet these objections, the leg was amputated at the hip joint, and all connections between the leg and the trunk except the femoral vessels and the sciatic nerve were severed. The femur was then tightly clamped in a vise, in such a position that neither the vessels nor the nerves were under tension. This procedure had the double advantage of making it possible to isolate the chemical from the nervous effects and also allowed one to make vigorous passive movements of the leg without causing any movement in the muscles proximal to the leg.

The results are shown in table 4. It can be seen from part A that even when the nerve and vessels were intact, the effects of passive motions were rather slight, being usually much less than in the previous experiments. This is to be attributed to the shock that necessarily ensues following amputation, and also to the fact that the mass of moving vessels was less in the amputated than in the intact legs. It is to be noted that, despite the smallness of the effect, the increase in ventilation occurred in each experiment. (The maximum error of measurement with the small spirometers used is not greater than 0.04 liter and in no instance was the increase in ventilation on passive movements less than three times this possible error.)

Following these observations the femoral vessels were occluded with bull dog clamps and the procedure was repeated (table 4, part B). Again, in each five instances an increase in ventilation resulted, although in dog G 13 this was scarcely greater than the error of measurement.

The clamps were then removed from the vessels, the sciatic nerve was cut and, after waiting a few minutes for the respiration to become constant, the procedure was repeated for the third time. In one experiment of the five a slight increase in ventilation resulted. In the remain-

ing four instances moving the leg, when the sciatic nerve had been cut, was without effect even though the blood supply was intact (table 4, part C). These observations seem to prove beyond question that the increase in ventilation produced by such movements is of reflex origin from the moving part.

7. The Rapidity of the Response of the Ventilation to Passive Movements: As can be seen in almost all charts, the increase in breathing usually occurred immediately after the beginning of passive movements. This fact is probably the most convincing evidence obtained that the effect was of reflex rather than of chemical origin.

8. The Return of the Ventilation to Normal After the Cessation of Passive Movements: In instances in which the increase in ventilation was of small degree the respiration often returned to the previous

TABLE 4.—*The Effect of Passive Movements of One Hind-Leg on the Ventilation of Dogs*

	A. Leg Amputated Except for Intact Femoral Vessels and Intact Sciatic Nerve			B. Femoral Vessels Clamped; Sciatic Nerve Intact			C. Sciatic nerve Cut; Femoral Vessels Intact		
	Ventilation per Minute, Liters			Ventilation per Minute, Liters			Ventilation per Minute, Liters		
Animal	Before Movements	During Movements	After Movements	Before Movements	During Movements	After Movements	Before Movements	During Movements	After Movements
G 10	3.20	3.38	3.16	3.22	3.34	3.24	3.44	3.52	3.48
G 11	3.58	3.79	3.64	3.86	4.00	3.83	3.85	3.82	3.82
G 12	2.30	3.05	2.35	2.64	3.19	2.77	3.81	3.77	3.67
G 13	4.26	4.41	4.23	4.15	4.19	4.03	2.98	2.76	2.57
G 14	2.02	2.26	2.04	1.82	2.06	1.78	1.62	1.60	1.60

control level as soon as the movements ceased. However, when a larger increase in ventilation occurred there was sometimes a "hang-over" effect, the respiration gradually returning to normal over a two or three minute period. This phenomenon was rather puzzling and led us to suspect that there might be a delayed chemical effect by means of alterations in the blood, as well as an immediate reflex effect. In order to test the matter, observations such as those depicted in chart 14 were made. This animal showed a definite increase in ventilation for at least two minutes after the cessation of the movements. Since there was no possibility in this instance of any blood from the leg returning to the general circulation, it is obvious that the delayed as well as the immediate increase in ventilation was due, in this instance at least, to nervous influences.

On second thought, this did not seem surprising. It has been shown by Garrey [12] that stimulation of a nerve ganglion produces an increase

12. Garrey, W. E.: The Action of Inhibitory Nerves on Carbon Dioxide Production in the Heart Ganglion of Limulus, J. Gen. Physiol. **3**:163, 1920.

in its metabolism, i. e., produces chemical changes in the ganglion. Hence one might expect a delayed return of the respiration to normal, for time might be required for reversal of the chemical changes induced by stimulation of the respiratory center, whether by reflexes or by other means.

The data that have been presented up to this point seem to indicate beyond question that muscular movements cause reflex stimulation of respiration. They show also that the nervous regulation of breathing is more sensitive than the chemical control. It is apparent that such respiratory adjustments as are made—whether the subject be a normal person or a sufferer from cardiac disease—to the ordinary muscular activities required by a sedentary routine existence are mediated through reflexes. In this regard the patient with cardiac disease and the normal person are similar; it remains for us to consider the respects in which they differ.

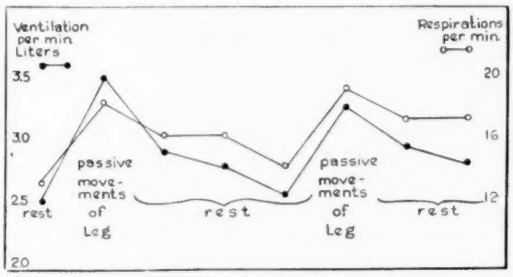

Chart 14.—The hind-leg of this dog was amputated except for the femoral vessels, and the sciatic nerve and the vessels were then clamped. Consequently the sciatic nerve was the only possible connection between the leg and the body. Passive movements of the leg resulted in an increase in respiratory rate and in ventilation not only during the movements but for two minutes afterward. The experiment indicates clearly that the increase in ventilation during the movements was of reflex origin, and that after the cessation of movements the delayed return of the ventilation to normal could only have been due to a continued action on the respiratory center of the changes induced in it by the previous stimulation from the reflex effect of the passive movements.

D. *Evidence that an Increase in Venous Pressure Produces Reflex Stimulation of Breathing.*—The data already reported seem to explain why, in the absence of chemical changes in the blood, muscular effort is accompanied by greater breathing. However, they do not explain why persons with cardiac disease usually have a greater increase in ventilation than do normal subjects on the performance of the same task. Bainbridge [13] demonstrated that a rise in pressure in the right auricle

13. Bainbridge, F. A.: The Influence of Venous Filling upon the Rate of the Heart, J. Physiol. **1**:65, 1915.

and great veins caused a reflex increase in pulse rate. It occurred to us that there might be a similar reflex effect on respiration, and this hypothesis was tested on dogs.

1. The Effect on Respiration of Increasing the Venous Pressure by Infusion of Fluid: In the first group of experiments the effect of

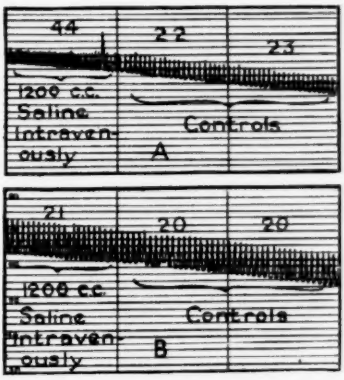

Chart 15.—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. Infusion of physiologic solution of sodium chloride caused a marked increase in respiratory rate and ventilation when the vagus nerves were intact (*A*) but not when they were cut (*B*).

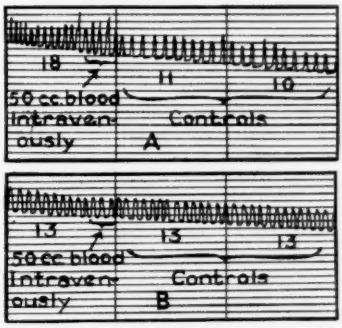

Chart 16.—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. Infusion of as little as 50 cc. of defibrinated blood caused a definite increase in respiratory rate and ventilation, provided the vagi were intact. *A*, vagi intact. *B*, vagi cut.

suddenly increasing the venous pressure by rapid infusions of fluid into the external jugular vein was noted. The results are shown in table 5 and in charts 15 and 16. Infusions of Ringer's solution, physiologic

solution of sodium chloride and blood all caused an increase in the ventilation and respiratory rate, provided the vagus nerves were intact. When the vagi were cut, no such effect was noted except when citrated blood

TABLE 5.—*The Effect on Respiration of Increasing Venous Pressure by Infusion of Fluid*

Animal*	Fluid Used	Amount of Fluid Injected, Cc.	Duration of Infusion, Seconds	Before Infusion		Immediately after Infusion		Vagus Nerves
				Ventilation per Minute, Liters	Respirations per Minute	Ventilation per Minute, Liters	Respirations per Minute	
1	Ringer's solution	1,200	60	4.55	26	7.12	42	Intact
2	Physiologic solution of sodium chloride	1,200	40	2.57	18	4.64	40	Intact
3	Physiologic solution of sodium chloride	1,200	80	2.28	22	3.19	44	Intact
	Physiologic solution of sodium chloride	1,200	80	4.14	20	4.34	21	Cut
4	Citrated blood	50	10	1.45	14	2.11	17	Intact
	Citrated blood	50	..	1.86	18	2.73	22	Intact
	Citrated blood	50	..	2.48	20	3.19	22	Intact
	Bled	300	180	3.19	22	2.46	17	Intact
	Citrated blood	50	10	2.96	11	4.64	14	Cut
	Citrated blood	50	10	4.06	14	5.64	17	Cut
5	Physiologic solution of sodium chloride	50	10	1.99	24	2.82	34	Intact
	Physiologic solution of sodium chloride	50	10	2.59	..	2.82	34	Intact
	Physiologic solution of sodium chloride	50	10	2.33	25	2.65	32	Intact
	Physiologic solution of sodium chloride	50	10	1.24	4	1.24	4	Cut
	Physiologic solution of sodium chloride	50	10	1.32	4	1.34	4	Cut
	Citrated blood	50	10	1.16	3	1.71	5	Cut
6	Defibrinated blood	50	10	1.37	11	2.28	22	Intact
	Defibrinated blood	50	10	1.62	13	1.59	13	Cut
15†	Physiologic solution of sodium chloride	50	10	1.66	16	1.66	16	Intact
	Physiologic solution of sodium chloride	50	10	2.04	19	2.07	20	Intact
	Physiologic solution of sodium chloride	50	10	2.16	13	2.16	13	Cut
16†	Physiologic solution of sodium chloride	50	20	1.58	17	1.41	17	Intact
	Physiologic solution of sodium chloride	..	20	1.49	18	1.57	19	Intact
	Physiologic solution of sodium chloride	..	20	1.36	6	1.42	6	Cut
17†	Physiologic solution of sodium chloride	50	15	0.91	11	0.91	11	Intact
	Physiologic solution of sodium chloride	50	15	1.49	12	1.37	12	Cut

* In the first six experiments the injections were made into the external jugular vein, with the cannula pointing toward the heart. In experiments 15 and 16 the injections were made into the same vein with the cannula directed away from the heart. In experiment 17 the cannula was in the inferior vena cava and pointed away from the heart.

† Reverse injection.

was used. It is evident that citrate causes chemical stimulation of breathing (animals 4 and 5, table 5). Defibrinated blood caused an increase in ventilation when the vagi were intact but no such effect when these nerves were cut.

These observations led us to believe that the increase in breathing was of reflex origin. In order to determine the source of the reflex, experiments were performed in which the pressure was raised in the veins but not in the heart. A cannula was inserted into the external jugular vein as far down as possible in the neck, and was directed away from the heart. Injecting fluid into the external jugular vein, and hence via the cerebral veins into the general circulation, had no effect on the breathing (table 5, animals 15 and 16). Similarly, when the cannula was placed in the inferior vena cava close to the diaphragm and pointed away from the heart, injecting fluid did not increase the ventilation (table 5, experiment 17). It therefore seemed probable that the

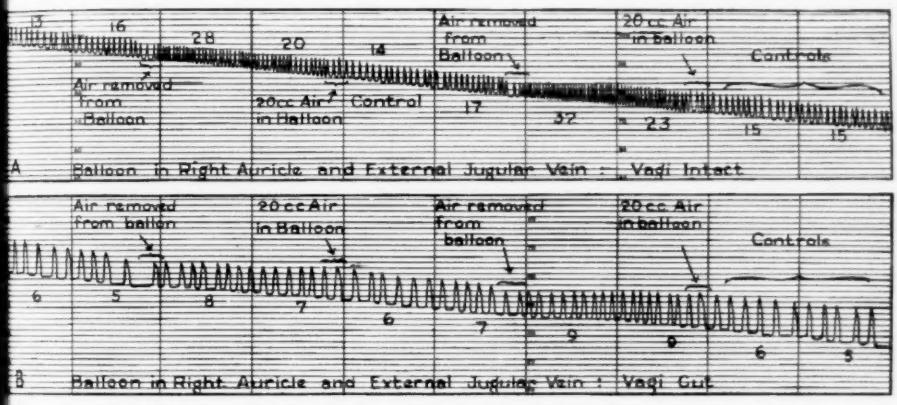

Chart 17.—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. *A*, inflation of the balloon with 20 cc. of air caused a well marked increase, and deflation caused a decrease of ventilation. *B*, after vagotomy the effects were much less striking.

respiratory response to injection of fluid was a reflex from the heart or from the great veins very near the heart.

2. The Effect on Respiration of Increasing the Venous Pressure by Distention of a Balloon in the Right Auricle: In order to test the matter further, additional observations were made. By means of a small rubber catheter and a condom an improvised empty balloon into which air could be injected was introduced into the right auricle either through the external jugular vein or through the inferior vena cava. The results are shown in table 6 and figure 17. So long as the vagi were intact, introducing air into the balloon caused an increase in ventilation and respiratory rate, whereas the reverse effects occurred when the air was removed from the balloon. When the vagus nerves were cut, the same procedures

either were without effect or produced much less striking results. (Bainbridge observed that vagotomized animals might show a slight response in pulse rate to a rise in venous pressure, the afferent path in this instance being by way of the sympathetic nerves. Some of our animals, even after vagotomy had a slight increase in respiration when the venous pressure was increased, but the effect was never marked and was often absent.)

TABLE 6.—*The Effect on Respiration of Increasing the Venous Pressure by Injecting Air into a Rubber Balloon in the Right Auricle*

Animal	Position of Balloon	Procedure	Before: Ventilation per Minute, Liters	Before: Respiratory Rate	After: Ventilation per Minute, Liters	After: Respiratory Rate	Vagus Nerves
7	Right auricle: external jugular vein	20 cc. of air in balloon.....	2.50	16	3.78	29	Intact
		Air removed from balloon	3.78	29	2.18	29	
		20 cc. of air in balloon.....	2.62	15	3.98	32	
		Air removed from balloon	3.98	32	1.88	14	
		20 cc. of air in balloon.....	1.88	14	3.37	28	
		Air removed from balloon	3.37	28	1.72	13	
		20 cc. of air in balloon.....	1.37	6	1.45	7	Cut
		Air removed from balloon	1.49	8	1.14	5	
8	Right auricle: inferior vena cava	10 cc. of air in balloon.....	1.87	41	2.18	48	Intact
		Air removed from balloon	2.18	48	1.87	41	
		10 cc. of air in balloon.....	1.87	41	2.23	49	
		Air removed from balloon	2.23	49	1.68	37	
		10 cc. of air in balloon.....	1.88	14	1.88	14	Cut
		Air removed from balloon	1.83	14	1.68	14	
		10 cc. of air in balloon.....	1.68	14	1.56	13	
		Air removed from balloon	1.56	13	1.56	13	
14	Right auricle: external jugular vein	20 cc. of air in balloon.....	2.48	48	3.53	57	Intact
		Air removed from balloon	3.53	57	1.87	41	
		20 cc. of air in balloon.....	1.87	41	3.62	53	
		Air removed from balloon	3.62	53	2.02	39	
		20 cc. of air in balloon.....	1.65	10	1.32	8	Cut
		Air removed from balloon	1.32	8	1.16	7	
		20 cc. of air in balloon.....	1.16	7	1.32	8	
		Air removed from balloon	1.32	8	1.16	7	
13	Right auricle: inferior vena cava	15 cc. of air in balloon.....	0.93	10	1.52	21	Intact
		Air removed from balloon	1.52	21	0.93	9	
		15 cc. of air in balloon.....	3.14	19	2.82	17	Cut
		Air removed from balloon	2.82	17	2.82	17	

The latter experiments indicate clearly that the increase in ventilation that occurred when fluid was injected could not have been due to augmentation of blood flow, as the balloon would tend to have the opposite effect. It seems clear that the increase in breathing is a reflex from the right side of the heart (and possibly from the cardiac ends of the great veins). The reflex is set off by an increase in the venous pressure or distention of the heart, or both, and its afferent path is through the vagus nerves.

These observations are in accord with those of Heymans and Heymans,[14] who demonstrated the existence of respiratory reflexes from the heart through the vagus nerves, and also with the findings of Sutton and Lueth,[15] who found that distention of the left ventricle caused dyspnea in the dog. Bainbridge recorded the respiration in some of his experiments, and did not observe marked changes on increasing the venous pressure. This may have been due to the fact that his animals received morphine, which tends to diminish the sensitivity of the respiratory center to stimulation.

E. *The Effect of Exertion on the Venous Pressure of Normal Subjects and of Persons with Cardiac Disease.*—The observations just reported indicate that a rise in venous pressure in the dog causes reflex stimulation of respiration. It occurred to us that such a reflex effect might furnish the explanation for the fact that persons with cardiac disease have a greater increase in ventilation than do normal subjects on performing the same exertion.

Schott [16] measured the rise in venous pressure in a series of persons before and after muscular exertion, which consisted of holding one leg upright until the subject became fatigued. He noted absent or minimal increases in normal persons, but patients with cardiac disease had a well marked rise in venous pressure. We have made somewhat similar observations which were carried out as follows:

The subject sat quietly in a comfortable chair for from ten to twenty minutes. A needle was inserted into the median basilic vein, minimal stasis being used. A series of readings of the venous pressure were then made according to the method of Moritz and Tabora.[17] Then, while an observer counted from a stop watch the subject moved the feet outward to two blocks 65 cm. apart and inward until the feet touched each other at a rate of thirty complete movements (out and in) per minute for two minutes. Measurements of venous pressure were made every thirty to sixty seconds during the exercise and for five minutes thereafter. The needle was then withdrawn from the vein, the face mask was put on and the ventilation was measured during corresponding rest and exercise periods. (At first we attempted to measure the venous pressure and the ventilation simultaneously, but because of the resistance to the face mask, which caused a slight but measurable rise in the venous pressure, it was found more satisfactory to measure the two functions separately.)

14. Heymans, C., and Heymans, J. F.: Stimulation et inhibition réflexes des mouvements respiratoires de la tête "isolée" du chien, Compt. rend. Soc. de biol. **95**:1118, 1926.

15. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827 (June) 1930.

16. Schott, E.: Die Erhöhung des Druckes im venösen System bei Anstrengung als Mass für die Functionstüchtigkeit des menschlichen Herzens, Deutsches Arch. f. klin. Med. **108**:537, 1912.

17. Moritz, F., and Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **93**:475, 1910.

Observations were made on three normal males and on five compensated and five mildly decompensated patients. The average results are shown in chart 18. It can be seen that the two functions, ventilation and venous pressure, exhibited a rather remarkable parallelism. The lowest values at rest during and after exertion were obtained in the normal subjects and the highest values occurred in the decompensated persons, the compensated patients being intermediate. The degree of rise in both functions during exercise was greater in the patients than in the normal persons. After exertion the venous pressure of the normal subjects rapidly fell to below the original resting level, whereas the venous pressure of the decompensated patients remained elevated for several minutes and again the compensated patients had an intermediate curve.

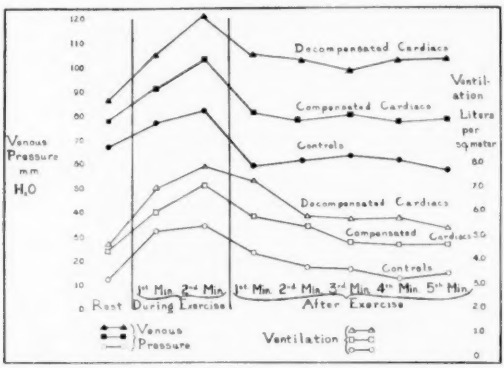

Chart 18.—The hollow symbols denote ventilation; the black symbols, venous pressure. In the patients with cardiac decompensation (which was of mild degree) both functions were greater at rest, underwent greater increase during exertion and returned to normal more slowly than was the case in the normal controls. The compensated cardiac patients were intermediate. The parallelism between the two functions—venous pressure and ventilation—in any given group is rather striking.

These observations are in agreement with those of Schott, who noted that exertion caused a greater rise in venous pressure in patients with congestive failure than in persons with compensated cardiac disease or in normal persons. Since we have shown that a rise in venous pressure causes, *per se*, a reflex increase in the ventilation, it seems probable that these observations furnish the explanation for the fact that muscular exercise of this type (i. e., not sufficiently severe to alter the composition of the blood) results in a greater increase in ventilation in persons with cardiac disease than in normal subjects.

COMMENT

The observations that have been presented seem to us to furnish a clear insight into the mechanism of the dyspnea that persons with cardiac disease feel on the performance of mild or moderate exertion.

First, the patient with heart disease has, in most instances, some diminution of the vital capacity. This means that for any given level of ventilation he is more likely to feel respiratory distress than would be the case if his vital capacity were normal (Peabody, and Harrison, Turley, Jones and Calhoun). Furthermore, the decreased vital capacity usually causes, through vagal reflexes from the lungs, some increase in the ventilation even at rest (Harrison, Calhoun, Cullen, Wilkins and Pilcher). This brings about still further diminution in the respiratory reserve and brings the patient close to, or in more severe cases across, the

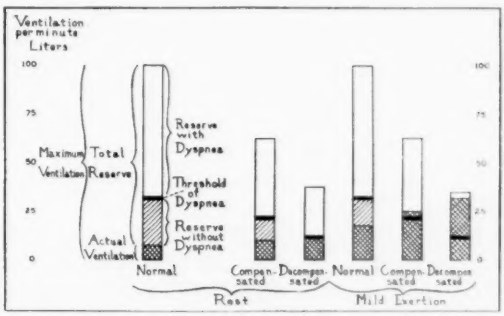

Chart 19.—This is a diagram and does not represent actual data. The assumed vital capacities are 4.0, 2.5 and 1.5 liters for the normal subject, compensated patient and decompensated patient, respectively. It is assumed also that the maximum possible ventilation per minute is twenty-five times the vital capacity, and that dyspnea appears when the minute ventilation is one third or more of its maximum. It is seen that at rest the normal subject has a large respiratory reserve. Because of decreased vital capacity and increased ventilation the reserve is smaller in the compensated patient, whereas the decompensated patient is, even at rest, using all of his "asymptomatic reserve" and feels slightly short of breath. The latter patient suffers severe dyspnea on exertion because he has only his "symptomatic" reserve to call on. The compensated patient, who was comfortable at rest, being below the threshold of dyspnea, becomes slightly short of breath with exertion because he uses up all his "asymptomatic reserve" and a little of his "symptomatic reserve." Even during the exercise the normal subject has a large "asymptomatic reserve" and experiences no dyspnea. (It is assumed that the exercise is mild and only sufficient to increase the resting ventilation by 150 per cent in each instance.)

threshold of dyspnea, while in the resting state. These conditions are shown diagrammatically in chart 19.

When muscular exercise is performed, there is an immediate reflex increase in the ventilation of both the normal subject and the patient,

due to afferent impulses from the moving muscles. After exercise has continued for a short time there is a further increase in ventilation in both subjects, due to the rise in venous pressure which also causes reflex stimulation of the breathing. Since the venous pressure does not rise immediately but gradually, the ventilation is less during the first than during the subsequent minutes of the exercise. The person with cardiac disease has a greater rise in venous pressure and hence has a greater increase in ventilation than does the normal subject. Following the cessation of exercise the ventilation of the normal person decreases rapidly and approaches the resting level within two or three minutes. During this short period it remains somewhat elevated because of "hang-over" effects (i. e., chemical changes induced in the respiratory center by the previous stimulation). In the patient with cardiac disease there is not only this factor but also the additional one of continued stimulation from the rise in venous pressure which persists for several minutes after the exercise. Hence the ventilation of such patients returns to the resting level more slowly than does that of normal persons. The greater increase in breathing is likely to cause the ventilation to exceed the threshold of dyspnea, which is lower than in the normal subject because of the diminished vital capacity. Respiratory distress results. This series of events is shown in the right-hand portion of chart 19.

Throughout this paper we have emphasized the importance of the reflex control of respiration. This does not mean that we are unmindful of the importance of the chemical control. In severe exercise the blood undergoes chemical changes which may play a dominant rôle in altering the respiration. However, our interest has been centered on muscular exertion of the degree corresponding to that which is necessary in the normal life of patients. To them their disorder is of serious consequence only when it interferes with their daily tasks. Except in the case of laborers, the amount of muscular activity that is necessary to carry on a useful life is not associated with chemical changes in the blood. Cardiac disease becomes crippling to the average patient when dyspnea develops on walking on the level or up a slight grade. The exercise that we have studied corresponds to such efforts and the dyspnea is clearly of nervous origin, being due to reflex respiratory stimulation from the muscles, the heart, the lungs and possibly other sites as yet unknown.

SUMMARY

Observations have been made in patients with cardiac disease concerning the causes of dyspnea produced by mild exercise. It has been shown previously that exertion of this grade is not associated with alterations in the chemical composition of the blood. The following results have been obtained:

1. The vital capacity, which was lower than normal in our patients, did not usually undergo further significant reduction on muscular effort.

2. The ventilation of patients with cardiac disease was greater at rest, rose more during exertion and remained elevated longer after exertion than was the case in normal subjects.

3. During active movements of the hands the ventilation increased whether or not the circulation to the hands was obstructed by inflated blood pressure cuffs around the upper portions of the arms. The effect of passive movements was similar to that of active movements.

4. In dogs passive movements of an extremity caused increased ventilation whether or not the circulation to and from the moving part was intact, but interference with the nerve supply of the moving part abolished the effect.

5. In patients with cardiac disease the venous pressure was somewhat higher at rest, underwent greater rise during exertion and remained elevated longer than that of normal subjects. The latter group exhibited a prompt fall in venous pressure to or below the resting level immediately after the cessation of exertion.

6. In dogs, raising the venous pressure either by infusions of fluid in the veins or by inflation of a balloon in the right auricle regularly caused an increase in ventilation so long as the vagus nerves were intact. When the vagi were cut, these procedures were usually without effect on the ventilation. Increasing the pressure in the great veins but not in the heart caused no effect on respiration, whether or not the vagi were intact.

From these observations the following conclusions are drawn concerning the mechanism of the production, in persons with cardiac disease, of dyspnea on mild exertion.

1. A decrease in vital capacity is important in two respects: (*a*) Per se, it lowers the respiratory reserve and thereby predisposes to dyspnea. (*b*) It increases the resting ventilation through vagal reflexes from the lungs and hence lowers the respiratory reserve still further.

2. Afferent impulses from the moving muscles play a rôle in the production of dyspnea because they caused reflex increase of the ventilation during the exertion.

3. Reflex stimulation of respiration, because of increased pressure in the right side of the heart and in cardiac ends of the great veins, is of especial importance: (*a*) In some cases venous pressure is higher than normal at rest and this increases the resting ventilation. (*b*) Venous pressure rises more than normally during exertion and hence the patient with cardiac disease has greater than normal ventilation during

exertion. (*c*) The venous pressure, in contrast to its behavior in normal subjects remains elevated after exertion, and therefore the ventilation in patients with cardiac disease also remains elevated longer than normal after the cessation of exercise.

4. All these factors so operate as to increase the value of the quotient $\frac{\text{ventilation}}{\text{vital capacity}}$, which is a measure of subjective respiratory distress in persons with cardiac disease.

5. These data constitute additional evidence against the validity of the widely accepted but erroneous theory that the symptoms of cardiac failure are essentially and primarily due to a diminution in the minute output of the heart.

LIVER FUNCTION IN HYPERTHYROIDISM

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Jaundice is an unusual complication of exophthalmic goiter. Isolated cases have been reported from time to time, and have been collected by Sattler.[1] Assmann [2] has more recently reviewed the subject and added his experience.

Clinical evidence of disturbance of the liver in hyperthyroidism is offered by occasional cases with frank jaundice. In most instances, icterus is unrelated to the disease and is merely the result of an intercurrent complication, such as catarrhal jaundice,[3] cholelithiasis,[4] syphilis,[5] cholangitis or other infections.[6] Cardiac decompensation and associated factors [7] may account for the appearance of icterus in the terminal stages of exophthalmic goiter. (In two cases of terminal jaundice complicating thyrocardiac disease observed by me, the jaundice was explained on the basis of cholangitis demonstrated histologically.) Occasionally, however, the jaundice can be explained only as a direct

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1. Sattler, T.: Basedowsche Krankheit, in Graefe-Saemisch: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1909, vol. 9, pt. 2, p. 263.

2. Assmann, H.: Leber und Milz bei Morbus Basedowii, München. med. Wchnschr. **78**:221 (Feb. 6) 1931.

3. (*a*) Eder, M. D.: Three Cases of Jaundice Occurring in Persons Suffering from Exophthalmic Goiter, Lancet **1**:1758 (June 23) 1906 (cases 1 and 2). (*b*) Chvostek, F.: Morbus Basedowii und die Hyperthyreosen, Berlin, Julius Springer, 1917.

4. Eder (footnote 3 a, case 3).

5. Habershon: Exophthalmic Goiter; Heart Disease; Jaundice; Death, Lancet **1**:510 (April 11) 1874. Gaill: Die Basedowsche Krankheit, Munich, 1883.

6. Chvostek (footnote 3 *b*). Mouriquand and Bouchut, cited by Assmann (footnote 2).

7. (*a*) Askanazy, M.: Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii, Deutsches Arch. f. klin. Med. **61**:118 (Sept.) 1898. (*b*) Rautmann, H.: Pathologisch-anatomische Untersuchungen über die Basedowsche Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:489, 1915. (*c*) Assmann (footnote 2: 2 cases).

influence of the thyroid intoxication on the liver cells.[8] In fact, extreme instances occur in which the course is that of an acute yellow atrophy [9] of the liver. Assmann emphasized an associated toxic action on the kidney in some cases with resulting albuminuria, which is not dependent on cardiac failure. He has also observed the retreat of the icterus with improvement in the thyroid condition.

Hepatic lesions have been discovered at necropsy in some cases of hyperthyroidism. They vary from fatty changes [10] to a fully developed atrophic cirrhosis.[11] Weller [12] has described an "interlobular chronic parenchymatous hepatitis," characterized by lymphocytic infiltration, bile duct proliferation and increased stroma in the islands of Glisson, in 50 per cent of forty-four postmortem cases of exophthalmic goiter. A control group of patients of the same age and sex showed an incidence (30 per cent) of minor pathologic changes in the liver almost equal to that of the thyroid group. The thyroid intoxication may possibly render the liver more susceptible to unrelated toxic agents.

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8. (*a*) Eger: Beitrag zur Pathologie des Morbus Basedowii, Deutsche med. Wchnschr. **6**:153, 1880. (*b*) Chvostek (footnote 3 *b*). (*c*) Pettavel, C. A.: Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:694, 1914.

9. Barker, L. F.: Thyreo-Intoxication with Necrosis and Atrophy of the Liver, Damage to the Heart Muscle and Kidneys, and Terminal Bronchopneumonia, M. Clin. North America **14**:261 (July) 1930. Hueck, cited by Assmann (footnote 2). Assmann (footnote 2). Raab, W., and Terplan, C.: Morbus Basedowii mit subakuter Leberatrophie, Med. Klin. **19**:1142 (Aug. 23) 1923. Kerr, W. J., and Rush, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, M. Clin. North America **6**:445 (Sept.) 1922.

10. Bodensteiner, F.: Beitrag zur Kenntnis des Morbus Basedowii, Munich, Kastner & Lossen, 1901. Jacoud, cited by Assmann (footnote 2).

11. (*a*) Sattler (footnote 1). (*b*) Eger (footnote 8 *a*). (*c*) Farner, E.: Beiträge zur pathologischen Anatomie des Morbus Basedowii mit besonderer Berücksichtigung der Struma, Virchows Arch. f. path. Anat. **143**:509 (March 9) 1896. (*d*) Mouriquand and Bouchut, cited by Assmann (footnote 2). (*e*) Paul, cited by Sattler (footnote 1). (*f*) Chvostek (footnote 3 *b*). (*g*) Askanazy (footnote 7 *a*). (*h*) Rautmann (footnote 7 *b*). (*i*) Landau: Pathological Histology of Basedow Struma, München. med. Wchnschr. **58**:1213 (May 30) 1911. (*j*) Neusser, cited by Sattler (footnote 1). (*k*) Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**:265 (Sept.) 1911. (*l*) Hueck, cited by Assmann (footnote 2). (*m*) Assmann (footnote 2). (*n*) Pettavel (footnote 8 *c*). (*o*) Wegelin, C.: Verhalten der übrigen Organe beim Morbus Basedowii und den Hyperthyreosen Schilddrüse, Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 402. (*p*) Matti, Goodpasture and Holst, cited by Wegelin.

12. Weller, C. V.: Hepatic Lesions Associated with Exophthalmic Goiter, Tr. A. Am. Physicians **45**:71, 1930.

Experimental observations of the effect of thyroid substance or thyroxine on the liver have revealed a disappearance of glycogen [13] and fatty changes involving especially the center of the lobule of the liver.[14] No hepatic functional impairment, as measured by the dye excretion test, could be detected by Youmans and Warfield [15] in dogs that had been fed a large amount of thyroid extract. Pettavel [8c] and Wegelin [11c] have noted livers absolutely devoid of glycogen in exophthalmic goiter.

Studies of hepatic function in hyperthyroidism have been based mainly on the results of the tetra-chlorphenolphthalein excretion test, the icterus index and sugar tolerance tests, with dextrose, galactose and levulose. Youmans and Warfield [15] found a retention of from 3 to 10 per cent of dye in the blood after sixty minutes in twenty-two of forty-eight cases and an elevated icterus index in seven of nine cases. Seven patients of the series were clinically jaundiced. However, their case notes indicate that in two of three fatal cases, with necropsy, a nutmeg liver due to chronic passive congestion existed; in the third case there was pneumonia, and in two nonfatal cases, auricular fibrillation. The results of the dye excretion test and the icterus index in these cases cannot be attributed to the hyperthyroidism.

Their studies in dextrose and levulose tolerance indicated a moderate degree of disturbance. They concluded, however, that there appeared to be no causal relationship between the degree of the liver damage and the disturbance in sugar tolerance. No correlation between the basal metabolic rate and functional impairment was apparent. There did seem to be some correlation between the loss of weight and the disturbance of liver function. This was interpreted as possibly due to the fact that in patients who had lost considerable weight an inability to maintain a satisfactory caloric intake developed.

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13. Cramer, W., and Krauss, R. A.: Carbohydrate Metabolism in Its Relation to the Thyroid Gland, Proc. Roy. Soc., London **86**B:550 (June 10) 1913. Cramer, W.: On the Glycogenic Function of the Liver and Its Endocrine Control, Brit. J. Exper. Path. **5**:128 (June) 1924. Parhon, M.: Sur la teneur en glycogene du foie et des muscles chez les animaux traités par des préparations thyroidiennes, J. de physiol. et de path. gén. **15**:75, 1913. Kuriyama, S.: The Influence of Thyroid Feeding upon Carbohydrate Metabolism: I. The Storage and Mobilization of the Liver Glycogen in Thyroid Fed Animals, J. Biol. Chem. **33**:193 (Jan.) 1918; The Influence of Thyroid Feeding upon Carbohydrate Metabolism, Am. J. Physiol. **43**:481 (July) 1917.

14. Farrant, R.: Hyperthyroidism: Its Experimental Production in Animals, Brit. M. J. **2**:1363 (Nov. 22) 1913.

15. Youmans, J. B., and Warfield, I. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, Arch. Int. Med. **37**:1 (Jan.) 1926.

In ten cases of exophthalmic goiter Kugelmann obtained evidence of a disturbance of hepatic function by means of a levulose tolerance test.[16] Alimentary galactosuria is often observed.[17]

Adler and Lemmel [18] have noted abnormal cholesterol ester partition in a few cases of severe exophthalmic goiter. The ester fraction was decreased as in cases of liver damage. They attributed the fatty stools sometimes observed in this disease to a disturbed fat metabolism.

The need for more sensitive methods of studying function of the liver cells has been stated repeatedly. Recently,[19] I reported a new method of estimating such function based on the colorimetric estimation of the excretion in the urine of oxy-cinchophen (2-[orthohydroxy]-phenyl-quinoline-4-carboxylic acid), an intermediary metabolite of cinchophen metabolism. In persons with normal function of the liver cells, less than 100 mg., or 21 per cent of the test dose, of cinchophen is excreted in this form. With a disturbance of hepatic function, larger fractions are excreted. The results of that study indicated that the disturbance in the metabolism of this choleretic substance might serve as a sensitive index of the function of liver cells. The present study was made on a series of twenty consecutive cases of hyperthyroidism. None of the patients, with the single exception of one with auricular fibrillation, gave any evidence of cardiac decompensation. A definite functional disturbance of the liver has been demonstrated in most of these cases.

METHODS EMPLOYED

The Brown modification of the Meulengracht method [20] was employed for the determination of the icterus index. In my experience the range for normal readings by this method lies between 6 and 8; the zone for latent icterus lies between 8 and 20, and that for hypobilirubinemia, between 2 and 6.

Urobilinuria was estimated by the zinc acetate method. Excretion in normal persons, as determined by this method, in my experience does not exceed 20 mg. daily.

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16. Kugelmann, B.: Ueber Störungen im Kohlhydratstoffwechsel beim Morbus Basedowii, Klin. Wchnschr. **9**:1532 (Aug. 16) 1930.

17. (*a*) Bauer, R.: Ueber die Assimilation von Galaktose und Milchzucker beim Gesunden und Kranken, Wien. med. Wchnschr. **56**:201. (*b*) Strauss, H.: Leberfunktionsstörungen bei Morbus Basedowii, Klin. Wchnschr. **9**:2441 (Dec. 27) 1930. (*c*) Hirose, M.: Ueber die alimentäre Galaktosurie bei Leberkrankheiten und Neurosen, Deutsche med. Wchnschr. **38**:1414 (July 25) 1912.

18. Adler, A., and Lemmel, H.: Zur feineren Diagnostik der Leberkrankheiten, Deutsches Arch. f. klin. Med. **158**:173 (Jan.) 1928.

19. Lichtman, S. S.: Cinchophen Oxidation Test of the Function of the Hepatic Cells, Arch. Int. Med. **48**:98 (July) 1931.

20. Brown, A. L.: A Rapid Clinical Method for the Determination of the Icterus Index, Arch. Path. **3**:409 (March) 1927.

Urobilinogenuria was determined with Ehrlich's aldehyde reagent, the Wallace and Diamond [21] dilution method for quantitative results being employed. In normal persons, by this method a dilution of 1:20 or less is considered normal.

Galactose tolerance was determined according to Bauer.[17a] Forty grams of galactose (Merck) was administered in 400 cc. of lemonade, and the urine was collected over a period of five hours. Sugar was estimated with Benedict's reagent, and a correction was made for copper reduction by galactose by multiplying by the factor 0.7. In normal persons, less than 3 Gm. of galactose is excreted in the course of six hours following its ingestion.

The presence of tyrosine in the urine was determined by the tyrosinase method.[22]

The cinchophen oxidation test of function of the liver cells was carried out as described elsewhere.[19] The standard dose of 0.45 Gm. of cinchophen was administered orally, and a quantitative fractional twenty-four hour specimen of urine was collected. The oxy-cinchophen content of each specimen was estimated colorimetrically by comparison with permanent standards prepared with a solution of 2- (orthohydroxy-phenyl) quinoline, 4-carboxylic acid (Calco). In persons with normal function of the liver cells, less than 100 mg., or 21 per cent of the test dose, is excreted in twenty-four hours in the form of oxy-cinchophen.

RESULTS

In the accompanying table are recorded the results of studies of the hepatic function and basal metabolic rates in a series of twenty cases of hyperthyroidism.

The icterus index was determined in seventeen cases. In three instances, increased readings, 10, 13 and 17, and 10, respectively, were obtained. In the second case, an encapsulated pleural effusion, with slight fever, possibly contributed to the latent icterus. In the other two cases no explanation of the latent icterus, other than the thyroid dysfunction, was evident. In six instances, hypobilirubinemia (icterus index, minus 6) was present.

Quantitative estimations of bilirubin by the van den Bergh method in eighteen cases failed to demonstrate an increased amount of bilirubin in the blood.

The galactose tolerance test, performed in sixteen cases, showed galactosuria in only three instances. In only one case, that of a diabetic patient with a glycosuria of 3.3 per cent preceding the test, was it excreted in abnormal amount (7.2 Gm.). In the other two cases, 2.5 and 1.8 Gm., respectively, were excreted. These results agree with those of Assmann,[2] who obtained negative results with the galactose test in cases of exophthalmic goiter with jaundice.

Estimations of the urobilin in the urine were made in nine cases. Increased daily excretions as high as 150 mg., 26 mg. and 115 mg.,

21. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35:** (June) 1925.

22. Lichtman, S. S., and Sobotka, H.: An Enzymatic Method for the Detection and Estimation of Tyrosine in Urine, J. Biol. Chem. **85:**261 (Dec.) 1929.

Results of Liver Function Studies and Basal Metabolic Rate in Twenty Cases of Hyperthyroidism

Case	Loss of Weight, per Cent; Time	Icterus Index	Blood Bilirubin, Mg.	Galactosuria	Urobilinuria	Urobilinogenuria Dilution	Oxycinchophen Excretion Mg.	Oxycinchophen Excretion Per Cent	Basal Metabolic Rate	Date of Test	Comments
1	33	4	0.2	0	Traces	1:5	108	22.5	40	4/ 9	Compound solution
A. J.	6 mos	6	0.3			1:10	122	25.5	40	4/13	of iodine 6/22; sub-
							68	14.0	..	....	total thyroidec-
							67	14.0	36	6/11	tomy 7/2
							82	17.0	17	6/25	
							82	17.0	5	7/14	
2	15.5	10	0.2	0	...	1:10	60	12.5	48	4/25	Hypertension; com-
H. W.	8 mos.	13					62	12.5	53	5/ 5	pound solution of
							153	32.0	55	5/10	iodine 5/8; subtotal
							118	24.5	..	....	thyroidectomy 5/18
							133	27.5	40	6/ 2	
							61	12.5	42	6/ 4	
3	11	17	0.2	0	0	....	145	30.5	89	3/ 4	Encapsulated
P. M.	7 wks.				36		...	....	81	3/ 5	pleural effusion,
							123	26.0	67	3/15	subfebrile; com-
							85	17.5	40	4/14	pound solution of
					150		86	17.5	30	4/24	iodine 4/4; subtotal
											thyroidectomy 4/16
4	20	8	0.4	...	...	....	148	30.5	42	2/ 8	Compound solution
S. S.	4 mos.	5					93	19.5	8	3/ 5	of iodine 2/9; sub-
											total thyroidec-
											tomy 2/19
5	0	7	0.2	0	26	....	161	33.5	47	2/10	Auricular fibrilla-
S. L.	1 yr.						139	29.0	48	3/10	tion; compound
							118	24.5	6	3/21	solution of iodine
							61	12.5	5	4/15	2/11; subtotal thy-
											roidectomy 4/6
6	?	6	0.2	2.5	115	Nega-	202	42.0	53	2/10	Compound solution
J. S.	5 mos.					tive	...	....	17	2/14	of iodine 2/11; sub-
							112	23.5	3	2/24	total thyroidec-
							157	33.0	20	3/10	tomy 2/26
							87	18.0	37	3/22	
7	14	4	0.2	...	...	Nega-	...	....	23	4/23	Compound solution
F. B.	6 mos.					tive	167	35.0	25	4/29	of iodine 4/29; sub-
							157	33.0	23	5/ 2	total thyroidec-
							132	27.5	5	....	tomy 5/7
8	20	3	0.2	0	Traces	Nega-	56	11.5	39	4/24	Compound solution
E. M.	4 mos.					tive	50	10.5	46	5/ 4	of iodine 4/25; sub-
							54	11.0	3	5/27	total thyroidec-
											tomy 5/7
9	36	4	0.2	0	0	Nega-	133	27.5	36	3/30	Compound solution
R. S.	9 mos.					tive	70	14.5	26	4/14	of iodine 4/8; sub-
							83	17.0	10	4/21	total thyroidec-
							78	16.0	6	5/ 5	tomy 4/23
10	20	10	0.3	0	...	....	127	26.0	34	12/12	Compound solution
M. S.	5 mos.						189	39.0	30	12/23	of iodine 12/9; sub-
							126	26.0	52	1/15	total thyroidec-
											tomy 12/26
11	18	6	0.2	0	Traces	1:5	145	30.5	27	5/ 1	Compound solution
P. S.	6 mos.				0		123	25.5	17	5/11	of iodine 5/5
							102	21.0	5	5/24	
							63	13.0	..	....	
12	?	8	0.2	...	...	....	47	10.0	40	2/18	Hypertension
J. A.	?						98	20.5	23	2/26	
13	15	2	0.2	0	...	....	86	17.5	26	2/19	
P. R.	1 yr.						141	30.0	29	3/ 4	
14	20	4	0.2	0	Traces	....	75	16.0	50	3/14	Acute thyrotoxi-
M. C.	5 mos.						67	14.0	50	3/19	cosis; necropsy
15	14	4	0.2	...	...	....	215	45.0	46	11/29	
S. B.	6 mos.										
16	20	..	0.2	0	...	....	...	....	18	6/ 3	Compound solution
P. B.	1 yr.						70	14.5	5	6/ 9	of iodine 6/5
17	7	6	0.2	1.8	...	....	116	24.0	28	2/18	
S. S.	9 wks.										
18	16.5	7	0.2	0	...	....	104	21.5	36	12/11	
B. B.	9 mos.										
19	.....	..	...	...	...	....	110	23.0	21	6/11	Diabetes mellitus
C. M.											
20	?	..	...	7.2	Traces	....	69	14.5	67	3/21	Diabetes mellitus;
P. S.	?						114	24.0	45	4/ 2	compound solution
											of iodine 3/31

respectively, were encountered in three cases. The first case was that of the patient with latent icterus (icterus index, 17), a subfebrile temperature and pleural effusion; the second, that of a patient with auricular fibrillation. The remaining instance may possibly be attributed entirely to the thyroid disease.

In two cases (cases 6 and 16, table) urine was examined for tyrosine, and it was not found.

The cinchophen oxidation test was carried out in every case. In sixteen of the twenty cases abnormal amounts of oxy-cinchophen were excreted in the urine in the twenty-four hour period. The largest excretions in the entire series were 215 mg. (case 15), 202 mg. (case 6) and 189 mg. (case 10). The patient who excreted 202 mg. had an attack of transient paroxysmal auricular fibrillation on the day of the test, which may have influenced the result. In the four cases (cases 8, 12, 14 and 16) with normal excretion of oxy-cinchophen, the results ranged between 50 and 75 mg. In nine of fifteen cases in which at least two estimations were made, the initial test made before treatment was instituted gave the highest excretion of oxy-cinchophen. In the five cases (cases 1, 4, 5, 9 and 11) in which the basal metabolic rate returned to normal after the administration of compound solution of iodine and after subtotal thyroidectomy or a period of rest, the excretion of oxy-cinchophen also dropped to normal. In four of seven cases (cases 2, 3, 6, 7, 10, 13 and 20) in which the basal metabolic rate remained elevated despite medical or surgical treatment, the excretion of oxy-cinchophen also remained elevated. In cases 2 and 3, in which the results of the cinchophen test became normal in spite of the elevated basal rates, reference to the table will indicate the atypical trend of excretion of oxy-cinchophen on repeated tests, and in case 3, the subfebrile course due to pleural effusion, which may be responsible for the persistently high metabolic rates.

In two cases (cases 19 and 20) of hyperthyroidism with diabetes mellitus 50 units of insulin was being administered during the test. Elsewhere [19] I have noted that in normal persons insulin decreases the excretion of oxy-cinchophen.

COMMENT

The excretory function of the liver as measured by bilirubinemia, icterus index, urobilinuria or urobilinogenuria did not appear to be impaired appreciably in this series of cases. In only two instances was there a latent icterus, and in one instance increased urobilinuria could be attributed to hyperthyroidism. Six patients had hypobilirubinemia (icterus index, minus 6). The apparent discrepancy with the results reported by Youmans and Warfield probably lies in the selection of cases. There was no case of frank jaundice and only a single case

of auricular fibrillation in my series of twenty consecutive cases. In this case, the icterus index was normal.

The galactose test gave normal results. In no instance was an alimentary galactosuria of pathologic significance encountered in this series.

The only consistent indication of impairment of hepatic function was obtained with the cinchophen oxidation test. In sixteen of the twenty cases, between 100 and 200 mg. of oxy-cinchophen, or from 21 to 42 per cent of the standard test dose, was excreted in the form of this intermediary metabolite of cinchophen metabolism. The figures indicate, in my experience, a slight impairment of function of the liver cells in the majority of cases, and in the remainder a moderately severe disturbance (between 150 and 200 mg. of oxy-cinchophen excreted daily, or from 31 to 42 per cent of the test dose). In no case was severe functional disturbance encountered. In case 14 (table), two tests made prior to a fatal attack of acute thyrotoxicosis gave normal results. The thyroid exacerbation followed an attack of acute tonsillitis with high fever and acidosis. There is not available at present information regarding the relationship of hepatic function to thyroid crises.

There was no relationship between the degree of functional hepatic impairment as measured by the cinchophen oxidation test and the basal metabolic rate. For a given case, however, there appeared to be in some cases a tendency for the function of the liver cells, as measured by this test, to improve as the basal metabolic rate returned to normal.

There is no apparent correlation between the loss of weight, the known duration of symptoms and the degree of impairment of function of the liver cells.

It might be contended that the increase in excretion of oxy-cinchophen here observed might be an expression of the general disturbance in bodily metabolism that occurs in hyperthyroidism. Other observations [19] have led me to believe, however, that the liver cell is responsible for the oxidation of cinchophen, that the normal organ oxidizes certain amounts of this substance at a fairly constant rate and that the appearance of larger fractions of the test dose of cinchophen in the form of oxy-cinchophen in the urine represents proportionate impairment of this metabolic function of the liver.

The depletion of glycogen in the liver in hyperthyroidism may be responsible for the impairment of the function of the liver cells that I have observed. The observations recorded elsewhere, that the administration of insulin diminishes the excretion of oxy-cinchophen and that there is a tendency toward an increase in the excretion of oxy-cinchophen in cases of carcinoma of the pancreas, lend support to the conception that the oxidation of cinchophen in the liver is influenced by its capacity to store and mobilize glycogen.

The extremely rare occurrence of frank jaundice in hyperthyroidism indicates that severe injury to the liver is unusual in this disease. Aside from chronic passive congestion of the liver associated with cardiac failure, intercurrent catarrhal jaundice, syphilis, cholelithiasis, cholangitis or intercurrent infections, there remain the silent forms of cirrhosis reported in this disease and the unusual cases of acute yellow atrophy. The latter complication has been observed so rarely that the question may properly be raised whether the association is not accidental, or perhaps also associated with the depletion of the glycogen content of the organ.

SUMMARY

A disturbance in the oxidation of cinchophen has been demonstrated in sixteen of twenty cases of uncomplicated hyperthyroidism. Thirteen of these cases showed an increased excretion of oxy-cinchophen in the urine up to 150 mg. daily. Larger amounts, between 150 and 200 mg., or from 31 to 42 per cent of the standard test dose, were excreted in the remaining three cases. On the basis of previous experience, this is believed to indicate moderate impairment of the capacity of the liver cell to oxidize this substance further. In no instance was severe impairment of hepatic function noted.

There was no apparent relationship between the degree of functional impairment of the liver and the basal metabolic rate, the known duration of the disease or the percentage of weight lost. In individual cases, however, there appeared to be a tendency for the function of the liver cells to improve as the basal metabolic rate returned to normal.

The constancy of depletion of glycogen in the liver cells in animals that have been fed thyroid substance and probably in clinical thyrotoxicosis suggests that the disturbance in oxidation of cinchophen is related to the capacity of the cells to store and mobilize glycogen.

The galactose tolerance test gave no indication of a disturbance of hepatic function.

There was little evidence of appreciable disturbance of the excretory functions of the liver as determined by studies on the icterus index, bilirubinemia, urobilinuria and urobilinogenuria.

BRANCH ARBORIZATION AND COMPLETE HEART BLOCK

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The mode of cardiac conduction has passed through a prolonged controversial siege, but has emerged as a proven entity. The bundle of His, formerly considered as a passive agent, has now been shown to be actively engaged in generating and discharging the impulses which result in ventricular contraction (Ishihara and Nomura [1]). Instrumental in formulating these conclusions has been the advent of the electrocardiograph. In animals, severance of the common bundle or one of its main branches has yielded specific tracings, but its application in man is still a matter of dispute.

NORMAL CONSIDERATIONS

Graphically, figure 1 shows what is now considered the normal course of impulses through the heart. From the sino-auricular node, situated at the junction of the superior vena cava and the appendage of the right auricle, fibers lead to: the superior vena cava (Wenckebach's bundle), to the inferior vena cava by way of the linea terminalis (Thorel's bundle) and to the auricular musculature. (A direct communication between the sino-auricular and the atrioventricular nodes has not been fully established, although Thorel [2] and Nomura and Ida [3] have described an indirect communication by way of the inferior vena cava and the coronary sinus.) At the base of the auricular septum, opposite the coronary sinus, lies the atrioventricular node, which collects fibers from the coronary sinus and the walls of the left and right auricles. The common bundle of His originates at this point and runs in the membranous portion of the intraventricular septum. The bundle divides at the anterior border of this membrane a little in front of the anterior attachment of the septal segment of the tricuspid valve. The left

Submitted for publication, May 12, 1932.
From the Department of Pathology, Cook County Hospital, Dr. R. H. Jaffé, Director.

1. Ishihara, M., and Nomura, S., quoted by Orr, J.: Oxford Medicine, New York, Oxford University Press, 1925, vol. 2, pt. 1, p. 371.

2. Thorel, C.: Ueber die supraventrikulären Abschnitte des sogenannten Reizleitungssystem, Verhandl. d. deutsch. path. Gesellsch. **14**:71, 1910.

3. Nomura, S., and Ida, H.: Histologic Researches on Connection Between Sinoauricular and Tawara's Node, Taiwan Igakkai Zasshi **283**:68, 1928.

division perforates the membrane at the upper border of the muscular septum beneath the union of the right and posterior leaflet of the aortic valve. Beneath the endocardium the left bundle divides into an anterior, medial and posterior branch (Kung [4]). Further divisions are extensive, and after sending branches to each of the papillary muscles of the mitral valve, the bundle breaks up into its arborizations.

The right division soon becomes subendocardial, courses downward to the moderator band and proceeds directly to the papillary muscle of the tricuspid valve, where it breaks up into its arborizations (Hill [5] and Lewis [6]). These arborizations communicate with the ventricular

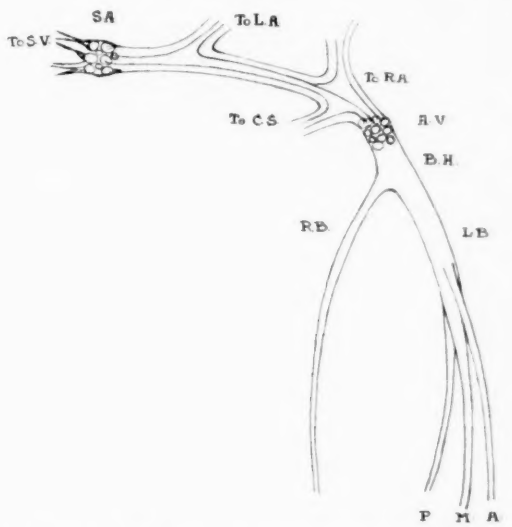

Fig. 1.—Schematic drawing of the entire conductive apparatus of the heart. (Modified after Kunz and Mobitz.) *S.A.* indicates sino-auricular node; *A.V.*, atrioventricular node; *B.H.*, bundle of His; *R.B.*, right branch; *L.B.*, left branch; (*P.*, posterior, *M.*, medial, *A.*, anterior divisions); *To S.V.*, to the superior vena cava; *To R.A.*, to the right auricle; *To L.A.*, to the left auricle, and *To C.S.*, to the coronary sinus.

musculature by the subendocardial network of the Purkinje fibers (Lewis [6]).

4. Kung, S. K.: Herzblockstudien; über die normalen Histologie des Reizleitungssystems und pathologisch-histologische Befunde an blockierten Herzen des Menschen, Arch. f. exper. Path. u. Pharmakol. **155**:295, 1930.

5. Hill, I. G. W.: Bundle Branch Block, Quart. J. Med. **23**:15, 1930.

6. Lewis, T.: Clinical Disorders of the Heart Beat, London, Shaw & Sons, Ltd., 1925; The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd., 1924.

Communications have been demonstrated between both auricles (Bachmann [7]) and both ventricles (Wahlin [8]).

BUNDLE BRANCH BLOCK

When one or the other division of the bundle of His is interrupted, the impulse is conveyed to the opposite ventricles not through the normal channel, but by spread through the musculature which unites the chambers (Lewis [6]). Thus, experimentally, severance of the right branch of the bundle of His will be designated in the electrocardiographic tracing as a levocardiogram (lead I: tall, broad and notched R, followed by a deep and rounded depression T; lead III: small summit R, followed by a broad notched extensive dip S and then a large rounded elevation T). Likewise, interruption of the left branch will be noted graphically as a dextrocardiogram (roughly the antithesis of a levocardiogram). The foregoing findings, originally described by Eppinger and Rothberger,[9] have been verified by Winterberg, Lewis,[6] Wilson and Herrmann,[10] Smith [11] and Eppinger and Stoerk.[12] Both dogs and monkeys were used in the experiments.

This overwhelming evidence questions the interpretations of Wilson, MacLeod and Barker,[13] who found that by applying the exploring electrode to the heart (over gauze soaked in a warm saline solution) severance of the left bundle gave a levocardiogram and lesions of the right bundle, a dextrocardiogram. This possibility was first suggested by G. Fahr [14] and later by Wilson, who worked on exposed human

7. Bachmann, G.: The Interauricular Time Interval, Am. J. Physiol. **41**:309, 1916.

8. Wahlin, B.: Direct Connection Between Purkinje's Network of Filaments of Both Ventricles Through Interventricular Septum, Upsala läkaref. forh. **34**: 769, 1928.

9. Eppinger, H., and Rothberger, J.: Ueber die Folgen der Durchschneidung des Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med. **70**:1, 1910.

10. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920; An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**:229, 1921.

11. Smith, F. M.: Further Observations on Experimental Lesions of the Branches of the Auriculoventricular Bundle of the Dog, Arch. Int. Med. **28**:453 (Oct.) 1921. Smith, K. S.: Coronary Thrombosis and Complete Heart Block, Lancet **1**:685, 1930.

12. Eppinger, H., and Stoerk, O.: Zur Klinik des Elektrokardiograms, Ztschr. f. klin. Med. **71**:157, 1910.

13. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, Am. Heart. J. **7**:305, 1932.

14. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**:146 (Feb.) 1920.

hearts. They concluded that the levocardiogram, which is usually interpreted as a left ventricular preponderance, should be called a right ventricular preponderance and vice versa. However, Oppenheimer and Stewart,[15] working under similar conditions, obtained opposite results. Furthermore, left ventricular hypertrophy by far outnumbers right ventricular hypertrophy, which corresponds to the relationship of levocardiograms to dextrocardiograms. It is a frequent occurrence in the autopsy room to verify levocardiograms obtained in cases of aortic regurgitation and essential hypertension.

MATERIAL

In five cases demonstrating lesions of the conducting apparatus, histologic studies were made of the entire circuit to determine the nature of the lesion. These were compared with their corresponding electrocardiographic tracings when available.

In case 1 the isolated lesion of the left branch of the bundle of His and its corresponding dextrocardiogram can be compared to an experimental study, and they aid substantially in establishing the original concepts of Eppinger and Rothberger.[9]

The number of cases of bundle branch block in which the electrocardiographic tracings have corresponded to the histologic observations is insufficient. Eppinger and Stoerk,[12] Cohn and Lewis [16] and Kauf have found levocardiograms in lesions of the right branch. However, Oppenheimer and Pardee [17] described one case in which the lesion was opposite to that predicted by the tracings, and Cohn and Lewis [16] found no lesions in a clinical branch block. These negative results do not necessarily refute the results of the experimental studies, as complete studies of both branches were not made.

Case 1.—*History.*—A strongly built colored man, aged 48, was "perfectly well" until five and one-half months before his death, when transient "fainting spells" suddenly developed. These were accompanied by a numbness of his hands and spots before his eyes. Nocturnal dyspnea was common. Five and one-half weeks before hospitalization, dyspnea and edema of the ankles set in.

On further questioning, he said that he had had precordial pain, which radiated to the right lower quadrant, a hard cough and a loss in weight of 20 pounds (9 Kg.).

15. Oppenheimer, B. S., and Stewart, H. J.: Dependence of the Form of the Electro-Cardiogram upon the Site of Mechanical Stimulation of the Human Ventricles, J. Clin. Investigation **3**:593, 1927.

16. Cohn, A. E., and Lewis, T.: A Description of a Case of Complete Heart-Block, Including the Post-Mortem Examination, Heart **4**:7, 1912-1913; The Pathology of Bundle Lesions of the Heart, Proc. New York Path. Soc. **14**:207, 1914.

17. Oppenheimer, B. S., and Pardee, H. E. B.: Site of the Cardiac Lesion in Two Instances of Intraventricular Heart-Block, J. A. M. A. **74**:1794 (June 26) 1920.

He had had rheumatism in 1914, which kept him in bed for eight weeks. A painful left knee had persisted. He said that he had not had chancre, but that he had had gonorrhea in 1896.

Examination.—On physical examination his pulse was found to be irregular, with a rate of 50 per minute; the respiratory rate was 26, and the blood pressure was 150 systolic and 50 diastolic.

His pupils were equal and regular, but reacted sluggishly to light. Both carotids and subclavian arteries pulsated visibly.

The heart was enlarged downward and to the left, giving an aortic configuration. There was a double murmur over the aortic area, which was of a soft and blowing character.

The Kahn reaction of the blood was 2 plus. Urinalysis and chemical analysis of the blood gave negative results. An x-ray picture of the chest verified the enlarged heart and aortic configuration.

The electrocardiographic tracing was interpreted as follows (Dr. H. J. Isaacs): ventricular rate, 45; auricular rate, 90; left bundle branch block; partial heart block (2:1), one ventricular extrasystole (lead I, fig. 2*c*).

The diagnosis was syphilitic aortitis with insufficiency and heart block.

Course.—While the patient was in the hospital, his radial pulse varied from 36 to 50 per minute. It was of good volume and was regular. His dyspnea, as well as his cough, continued, but syncope did not appear. Gradually, he became more dyspneic; his pulse became weak and thready, and finally, restlessness, a cold and clammy skin and fear of approaching death were present. His pulse rate preceding death was 44 per minute.

Postmortem Examination (Dr. R. H. Jaffé).—The body, weighing 170 pounds (77.1 Kg.) and being 188 cm. in length, was that of a tall, strongly built colored man whose oral mucosa was purple gray.

The heart (fig. 3) weighed 580 Gm. The epicardium was smooth and shiny. The transverse sinus was distended and filled with blood. The apex was formed by the left ventricle. The wall of the left ventricle measured 18 mm. in thickness, while that of the right was 8 mm. The myocardium was light purple brown and friable. The right leaflet of the aortic valve was diffusely thickened, especially in its medial and lower portion. The commissure with the left leaflet was thickened, greatly deformed and grayish white. The sinus of Valsalva of the right leaflet was transformed into a large sac, which extended into the ventricular septum. This sac measured 42 mm. in its transverse and 35 mm. in its vertical diameter. The wall, which separated the sac from the ventricular lumen, was composed of a firm light yellowish-gray tissue. This tissue fused with the aortic leaflet. The inside of the sac was lined by a grayish-white, firm, adherent membrane. In the lower third of the sac was an irregular opening with shaggy edges, 14 by 11 mm. in diameter, which connected the lumen of the sac with the left ventricle. The endocardium over the septum adjacent to the sac was thickened and yellow white.

The aorta measured 75 mm. (1 cm. above the aortic cusps). In the arch there were small grayish-white areas with irregular wrinkling and puckering. In the ascending and descending portions the intima was smooth except for a few calcific plaques.

The coronary arteries were thin-walled and had smooth intimas, except for an occasional yellow plaque up to 4 mm.

The remaining organs showed evidence of passive congestion.

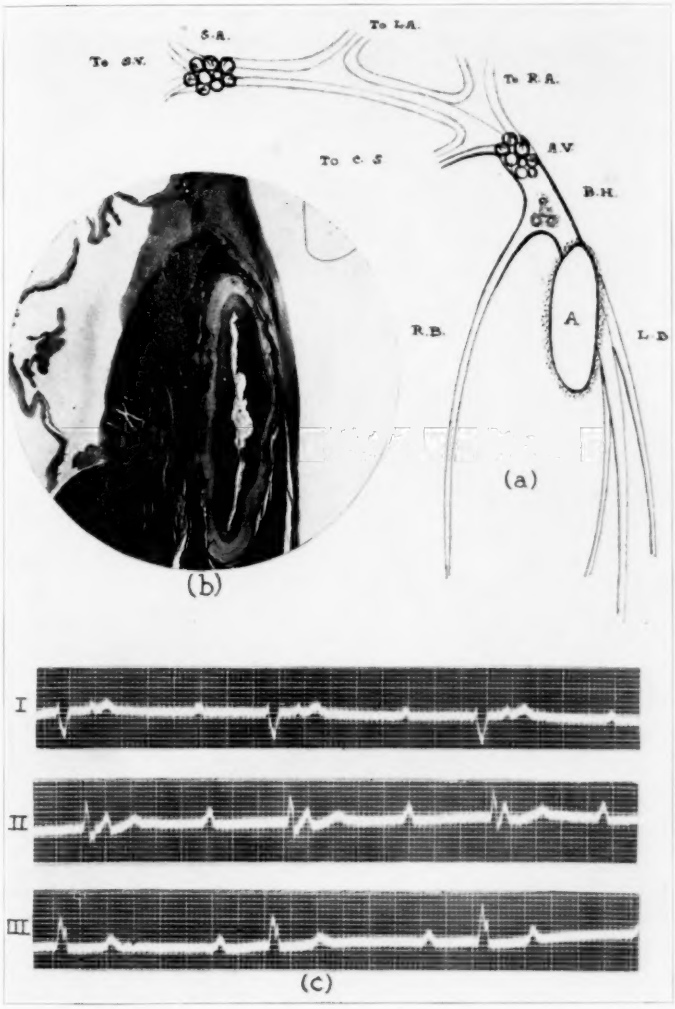

Fig. 2.—In *a* is a schematic drawing showing the interruption of the left branch of the bundle of His by the aneurysmal sac (*A*). *b* is a photomicrograph showing the same (reduced from × 6). *c* shows electrocardiographic tracings (three leads, showing a 2:1 heart block and a left bundle branch block.

Microscopic Data.—Intraventricular Septum, Including the Posterior Aspect of the Right Auricle (fig. 2, *a* and *b*): The aneurysm, described grossly, extended into the septum and occupied the left half, while the right half appeared well preserved. The upper limit of the sac was 2 mm. below the bundle of His, and it extended downward for a distance of 10 mm. Over this extent the left wall of the sac interrupted the left bundle, save for a few strands. The remaining fibers of the left branch of the bundle of His were loosened, broken up in places and

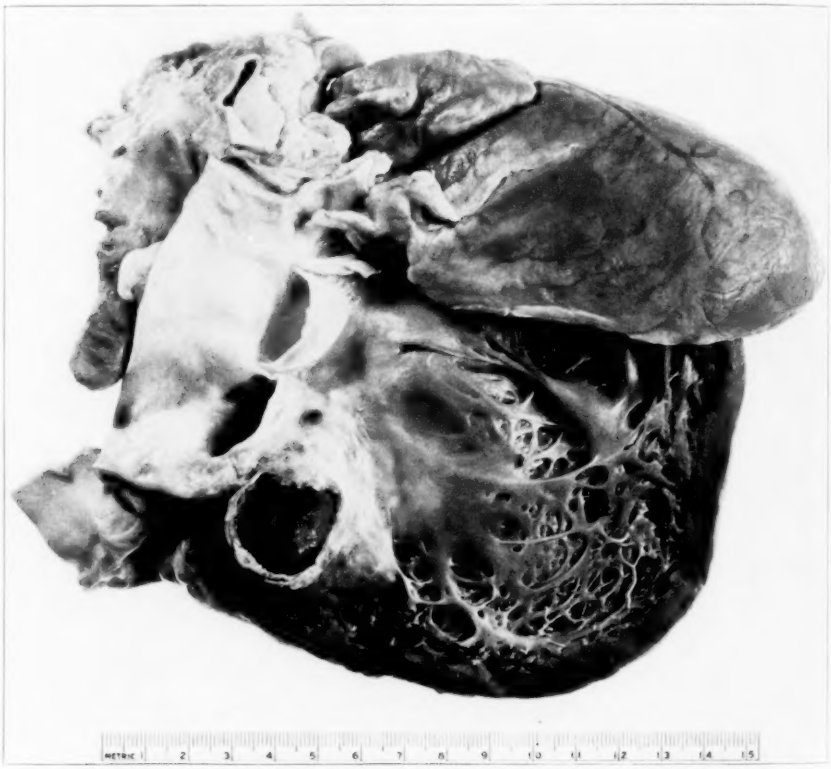

Fig. 3.—Aneurysm of the right sinus of Valsalva rupturing into the left ventricle.

infiltrated by lymphoid round cells and plasma cells. The cavity was lined by a membrane 2 mm. in thickness, the outer aspect of which was composed of dense connective tissue with long fusiform cells which often contained fine, light brown pigment granules. The inner aspect was lined by a layer of hyalinized fibrin with histiocytic elements and small round cells. About the wall of the aneurysm was a dense infiltration by small round cells, plasma cells and histiocytes, filled with a light brown pigment.

The right branch of the bundle was separated from the sac by a 3 mm. layer of muscle the fibers of which were moderately hypertrophic, and there was no interruption of their continuity or round cell infiltration. The right branch proper was well preserved. In the region of the bundle of His, there were small arteries which showed a distinct thickening of their walls as a result of intimal proliferation, in some instances obliterating the lumens. Their adventitia and periadventitia were infiltrated by small round cells. In the region of the sino-auricular and the atrioventricular nodes and the posterior wall of the right auricle no abnormal changes were seen.

Aorta: The adventitia was thickened by an increase in fibrous tissue and accumulations of round cells. The walls of the vasa vasorum were thickened and were surrounded by lymphoid round cells and plasma cells. The entire extent of the media was penetrated by numerous young capillaries with round cell cuffs. There was marked scarring of the media about the capillaries or independent of them. The intima was thickened and presented hyalinic plaques.

TABLE 1.—*Summary of Case 1*

Diagnosis			
Pathologic		Clinical	Electrocardiographic
Sino-auricular node	No change	Syphilitic aortitis with insufficiency and heart block	Left bundle branch block; partial heart block (2:1)
Auricular fibrils	No change		
Atrioventricular node	No change		
Common bundle of His	Marked perivascular round cell infiltration with endarteritis		
Left branch	Complete interruption by aneurysmal sac with marked round cell infiltration		
Right branch	No change		
Arborization	No change		
Comment		Kahn reaction of blood ++	

Anatomic Diagnosis.—This was: aneurysm of the right sinus of Valsalva of the aortic valve, extending into the interventricular septum and perforated into the left ventricle; interruption and compression of the left branch of the bundle of His by the aneurysm; eccentric hypertrophy of the heart; syphilitic aortitis; passive congestion of the lungs, liver, kidney and spleen.

The foregoing case is rare not only in its isolated affectation of the left branch of the bundle of His, but also as a purely pathologic entity. Only five cases of aneurysm of the sinus of Valsalva have been reported (Castellano and Maldonado Allende,[18] Sheldon,[19] Marty and Froncin[20]

18. Castellano, T., and Maldonado Allende, I.: Aneurysm of the Sinus of Valsalva and of the Thoracic Aorta Co-Existing with Syphilis of the Lungs, Prensa méd. argent. **17**:346, 1930.

19. Sheldon, J. H.: A Case of Aneurysm of a Sinus of Valsalva Bursting Externally, Lancet **1**:178, 1926.

20. Marty, P., and Froncin, J.: Petit anévrisme du sinus de Valsalva démeure latent et rompu secondairement dans le péricarde; coexistence de lésion d'endocardite ulcéro-végétante, prédominant d'l'orifice aortique, Bull. et mém. Soc. méd. d. hôp. de Paris **94**:580, 1924.

and Roth.[21]). In three cases the aneurysm extended outwards, and in two instances it ruptured into the pericardial sac, causing a heart tamponade and death. Of Roth's two cases, in one the aneurysm compressed the interauricular septum, with a loss of continuity of the bundle of His. In the other, the lesion pressed on the arterioventricular node, but produced no microscopic changes in it. Cohn and Lewis [16] described an aneurysm originating from the posterior aspect of the left ventricle at the base of the heart, extending beneath the aortic valves into the interauricular septum. The atrioventricular node was thus separated from the bundle of His. Both branches were also affected by a fibrotic process. Syphilis was the etiologic factor, but the aorta showed only atherosclerotic changes. Their patient was a white man, aged 46, who had a Stokes-Adams syndrome and a pulse rate of 30 per minute.

ARBORIZATION BLOCK

Extensive subendocardial scarring involving the terminal branches of the bundle of His supposedly produces electrocardiographic tracings similar to those of bundle branch block except that the voltage is low. This condition was termed arborization block by Oppenheimer and Rothschild [22] and was confirmed by Willius.[23] Experimentally, it was not possible to produce such lesions by scarifying the entire endocardium. Only by cutting one of the main stems of the bundle in addition to the scarification were graphs obtained similar to those described by Oppenheimer and Rothschild (Wilson and Herrmann,[10] Brinck, Miszke and Schöne,[24] Rothberger and Winterberg,[25] Smith [11] and Master and Pardee [26]).

Coronary sclerosis with infarction and chronic myocarditis with scarring are the pathologic processes mentioned which will produce arborization blocks. It is impossible to perceive that such lesions will

21. Roth, O.: Zur Kenntnis der Ueberleitungsstörungen des Herzens, Deutsches Arch. f. klin. Med. **112**:104, 1913.

22. Oppenheimer, B. S., and Rothschild, M. A.: Abnormalities in the Q R S Group of the Electrocardiogram Associated with Myocardial Involvement, Proc. Soc. Exper. Biol. & Med. **14**:57, 1916; Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

23. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (April) 1919.

24. Brinck, J.; Miszke, B., and Schöne, G.: Zur Klinik und Pathologie "des Arborisation Block" (Astblock), Deutsches Arch. f. klin. Med. **169**:129, 1930.

25. Rothberger, C. J., and Winterberg, H.: Ueber die Beziehungen der Herznerven zur atrio-ventrikulären Automatie, Arch. f. d. ges. Physiol. **135**:559, 1910; Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Säugetierherzens, Ztschr. f. d. ges. exper. Med. **5**:264, 1917.

26. Master, A. W., and Pardee, H. E. B.: The Effect of Heart Muscle Disease on the Electrocardiogram, Arch. Int. Med. **37**:42 (Jan.) 1926.

affect the subendocardium only. Usually the myocardium generally is involved, including the bundle branches. One finds diffuse thickening of the subendocardial region with only slight changes in the myocardium in cases of long-standing dilatation of the heart (rickets, prolonged thyrotoxicosis and debilitating diseases). In none of the foregoing instances were arborization blocks noted.

The explanation of the electrocardiographic tracings in the so-called arborization block is as follows: The widening and notching of the Q-R-S complex are a result of a branch lesion, while the low voltage is the result of the severe myocardial damage also affecting the arborizations. The bases for these conclusions are found in case 2, in which a coronary sclerosis had produced a complete fibrous interruption of the right branch and, to a great extent, the left branch. A more recent coronary thrombosis had caused a complete infarction of the myocardium of the interventricular septum, also affecting the arborizations (fig. 4).

Case 2.—*History.*—A white man, aged 54, an American, was in fair health until two weeks before his death, when, while lying in bed, he fainted. The attack was momentary, but recurred a few hours later. He was brought to the hospital fully recovered and alert. On questioning, he said that he had not had any previous attacks, but that he had had hiccups, nausea and vomiting on the day preceding the syncope. At no time did he experience precordial or epigastric distress. During the past year he had noticed numbness in his toes associated with a dull boring to burning pain. This was most marked on exertion, but at best was not alarming.

Examination.—On physical examination, the patient was found to be slightly dyspneic, but he did not appear acutely ill. His temperature was 99.4 F.; the pulse rate was 100 per minute; the respiratory rate, 24 per minute, and the blood pressure, 100 systolic and 70 diastolic.

The findings generally were not startling. There were moist râles in the base of the right lung posteriorly. The heart was not enlarged; the tones were equal and regular, but of only fair volume. The liver was enlarged and extended 4 cm. beneath the right costal margin.

The extremities were numb and cold, and pulsations of the dorsal pedis artery were absent. There was no edema of the ankles.

The Kahn reaction of the blood was negative; the white blood count was 12,200; the urine was normal.

The electrocardiographic tracing was interpreted as follows (Dr. H. J. Isaacs): rate, 125; somatic tremor, low voltage and notching of Q-R-S complexes; myocardial degeneration; T1 positive and T2 iso-electric; bundle branch lesion suggested, perhaps due to coronary disease—arborization block (fig. 4*c*).

The diagnosis was coronary thrombosis with a secondary bundle branch lesion and arborization block.

Course.—While the patient was in the hospital, he had frequent liquid, bloody stools, but he did not complain of pain. Singultus continued day and night. His pulse rate varied from 95 to 120 per minute; it was of fair volume and regular. Terminally, marked dyspnea, cyanosis and profuse diaphoresis developed.

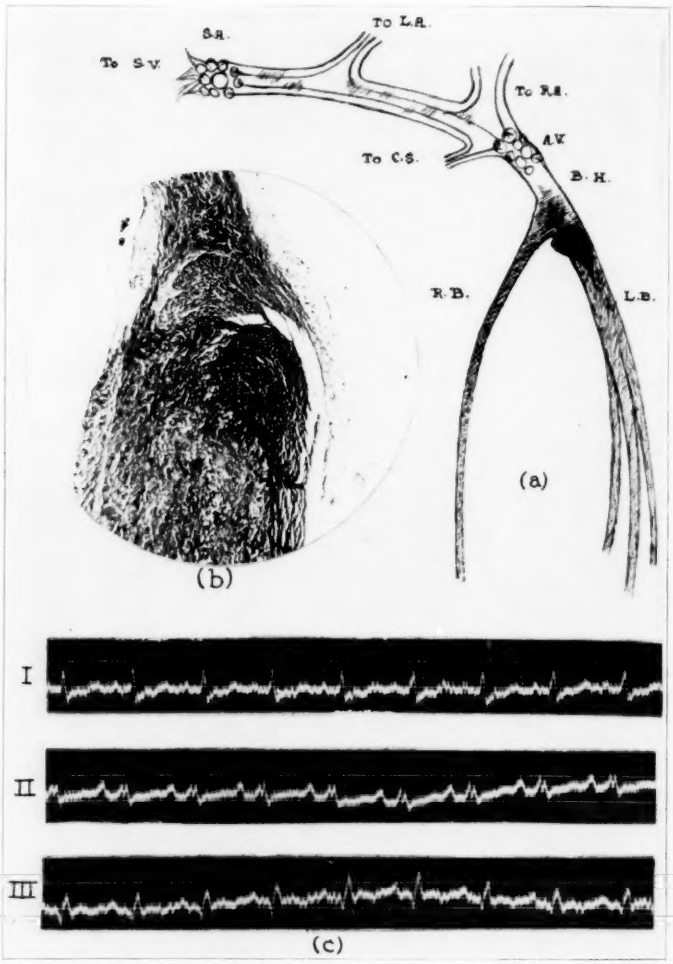

Fig. 4.—In *a*, the dark shading represents fibrosis which has interrupted the right branch of the bundle of His, and also the left branch except for a few fibers. The light shading represents necrosis of the smaller divisions of both branches. *b* is a photomicrograph in the region of the bifurcation of the bundle of His (reduced from × 30). Note the single muscle fibers extending about the outer aspect of the dense fibrotic area. These fibers were evidently sufficient to transmit impulses along the left branch. *c* is an electrocardiographic tracing showing low voltage and a notching of the Q-R-S complexes. Thus the diagnosis of an arborization block and a bundle branch lesion was made.

Postmortem Examination (Dr. S. R. Rosenthal).—The body, weighing 140 pounds (63.5 Kg.) and being 167 cm. in length, was that of a strongly built white man; the skin of the neck and chest was discolored a deep purple.

The pericardial sac contained 100 cc. of a reddish-brown fluid. The epicardium was injected and covered by a fine, fibrinous exudate.

The heart weighed 430 Gm. The left ventricular wall measured 13 mm., and the right ventricular wall, 3 mm. The myocardium was light red brown, extremely soft and friable. At the apex of the left ventricle the wall was suddenly reduced to 4 mm., as the myocardium had lost its normal structure and was very soft. In an area 1 cm. in diameter on the anterior aspect of the left ventricle, only the thickened epicardium remained. The internal aspect of the myomalacic site was lined by a reddish-gray, firmly adherent thrombus. The interventricular septum, beneath the membranous portion, for a distance of 5 cm. in diameter, was transformed into a homogeneous dirty grayish-brown mass which extended through the entire wall and caused slight erosions of the endocardium of both ventricles.

TABLE 2.—*Summary of Case 2*

Diagnosis			
Pathologic		Clinical	Electrocardiographic
Sino-auricular node....	No change	Coronary thrombosis	Low voltage and notching of Q-R-S complexes; myocardial degeneration; T1 positive and T2 iso-electric, suspect bundle branch lesion perhaps due to coronary disease; arborization block
Auricular fibrils.....	Moderate fibrosis		
Atrioventricular node..	No change		
Common bundle of His	Moderate fibrosis with calcification		
Left branch.....	Marked fibrosis with interruption except for a few strands		
Right branch.....	Complete interruption by dense fibrous tissue		
Arborizations.....	Complete necrosis		

Both of the coronary arteries were tortuous and pipe-stemlike. The left one contained a small reddish-gray thrombus at its mouth which seemed to occlude the lumen completely. The right coronary artery was similar, except at its mouth, where a light yellowish-brown, atheromatous material seemed to obstruct it.

The aorta presented diffuse arteriosclerotic plaques up to 2 cm. in diameter. In the abdominal portion, the lumen was almost completely occluded by a grayish-white thrombus which was moderately adherent to the wall. Beneath the thrombotic mass, the intima was studded by atherosclerotic ulcerations. The aortic thrombus extended into both iliac and femoral arteries, where it appeared well organized and practically occluded the lumens.

To account for the bloody stools, there was an annular area 3 cm. wide at the sigmoid rectal junction, which was entirely necrotic and yellow green. A large vessel leading to this junction was occluded by a reddish-gray thrombus. The descending colon above this portion was the site of longitudinal ulceration up to 10 cm. long and 1 cm. wide.

Microscopic Data.—Interventricular Septum Including the Posterior Wall of the Right Auricle (Fig. 4 *a* and *b*): The atrophic myocardium of the auricle was densely interspersed with broad fibrous tissue bands. In the region of the atrioventricular node were large elongated cells with round or oval nuclei and ample sarcoplasm. The sarcoplasm stained a yellow brown with the van Gieson method

This accumulation of cells showed no abnormal changes, although surrounding it were small foci of calcification and fibrosis.

Immediately beneath the membranous portion of the septum was a small, well isolated triangular area of muscle fibers that showed marked atrophic changes and interstitial fibrosis. This area was completely surrounded by dense fibrous tissue except for a few thin muscle strands that joined the subendocardial region of the left ventricle. The entire circuit stained a light yellow brown with the van Gieson stain. The continuity of the triangular area to the subendocardial region of the right ventricle was interrupted by dense fibrous tissue. The remaining septum showed a complete necrosis of the muscle fibers corresponding to the gross appearance.

Anatomic Diagnosis.—This was: Severe coronary sclerosis with thrombosis of the left coronary artery and atheromatous occlusion of the right coronary artery; myomalacia of the wall of the left ventricle and interventricular septum; severance of the right branch of the bundle of His by dense fibrous connective tissue; interruption of the left bundle of His by dense fibrous tissue except for a few fibers, which were intact; recent serofibrinous pericarditis; severe atherosclerosis of the aorta with thrombotic occlusion of the entire abdominal portion and of both iliac and femoral arteries; infarction of a branch of the inferior mesenteric artery with necrosis of a segment of the sigmoid colon and stercoral ulcers above this point.

COMPLETE HEART BLOCK

Experimentally as well as clinically, complete heart block may be produced in the following manner: by interference with the conducting tracts, namely, the atrioventricular node and the bundle of His or its branches; by vagus stimulation (the left vagus because its action is more direct to the atrioventricular node), and by the introduction of toxic substances into the blood stream (digitalis, muscarine, diphtheria toxin and other substances, Lewis [16]).

Interference with the conducting apparatus has been described, resulting from inflammatory, vascular, degenerative, neoplastic, traumatic or congenital causes. Very little has been written regarding the pathogenesis of heart block in essential hypertension. The following case demonstrates the end-results of a hypertensive heart in which the coronary arteries were grossly normal.

CASE 3.—*History.*—A white man, aged 70, had been in and out of the hospital several times during a two year period. He complained of precordial pain, dyspnea on exertion and edema of the ankles.

Examination.—On physical examination he was found to be well nourished and developed and, though comfortable, had a regular pulse rate of 36 per minute. His blood pressure was 182 systolic and 64 diastolic.

The heart was markedly enlarged, with the left border in the anterior axilliary line. A soft systolic blow was heard at the apex. The tones were weak but regular and slow (36 per minute).

The lungs were normal except for fine moist râles in the bases.

The liver was tender and slightly enlarged.

The lower extremities and genitalia were markedly edematous.

The electrocardiographic report read as follows (Dr. H. J. Isaacs): ventricular rate, 50; auricular rate, 90; left ventricular preponderance; marked myocardial degeneration, and a few ventricular extrasystoles. Lead II showed evidence of a complete heart block (fig. 5*c*).

The diagnosis was hypertensive heart with decompensation and complete block.

Course.—The patient was digitalized and quickly improved. He left the hospital only to return shortly afterward with cardiac decompensation. These measures were repeated several times. Finally, he entered the hospital with similar complaints one month before his death. His heart rate varied from 40 to 48 per minute. The electrocardiographic tracings were unchanged.

Decompensation was severe, with râles in the bases of both lungs, tenderness of the liver and marked dependent edema. The patient was cyanotic; his lungs were filled with loud bubbling râles, and he complained frequently of cardiac pain.

TABLE 3.—*Summary of Case 3*

	Diagnosis		
	Pathologic	Clinical	Electrocardiographic
Sino-auricular node		Hypertensive heart disease with decompensation and complete heart block	Marked myocardial degeneration and complete heart block
Auricular fibrils			
Atrioventricular node			
Common bundle of His	Fibrous and fatty changes with calcific deposits		
Left branch	Completely interrupted by dense fibrous tissue and calcific deposits		
Right branch	Completely interrupted by dense fibrous tissue and calcific deposits		
Arborizations	Moderate subendothelial fibrosis of right and left ventricle		
Comment		Blood pressure 182 systolic and 64 diastolic (when decompensated)	

Venesection proved of no avail. In this state the patient died, two years after the first observation.

Postmortem Examination (Dr. R. H. Jaffé).—The body, weighing 185 pounds (83.9 Kg.) and being 171 cm. in length, was that of a well nourished white man whose face was cyanotic and whose lower extremities and scrotum were markedly edematous.

The heart weighed 700 Gm. The epicardium over the lateral aspect of the left ventricle was slightly thickened; otherwise, it was smooth and shiny. The wall of the left ventricle measured 16 mm., while that of the right ventricle was 6 mm. The myocardium was a light purple brown, mottled with purple gray. Both chambers were dilated, the trabeculae carneae being flattened. The endocardium appeared unchanged.

The coronary vessels were thin-walled, and the intima of the circumflex branch of the right side contained single, small, light yellow plaques.

The spleen and the liver showed signs of long-standing passive congestion. There were no other important findings.

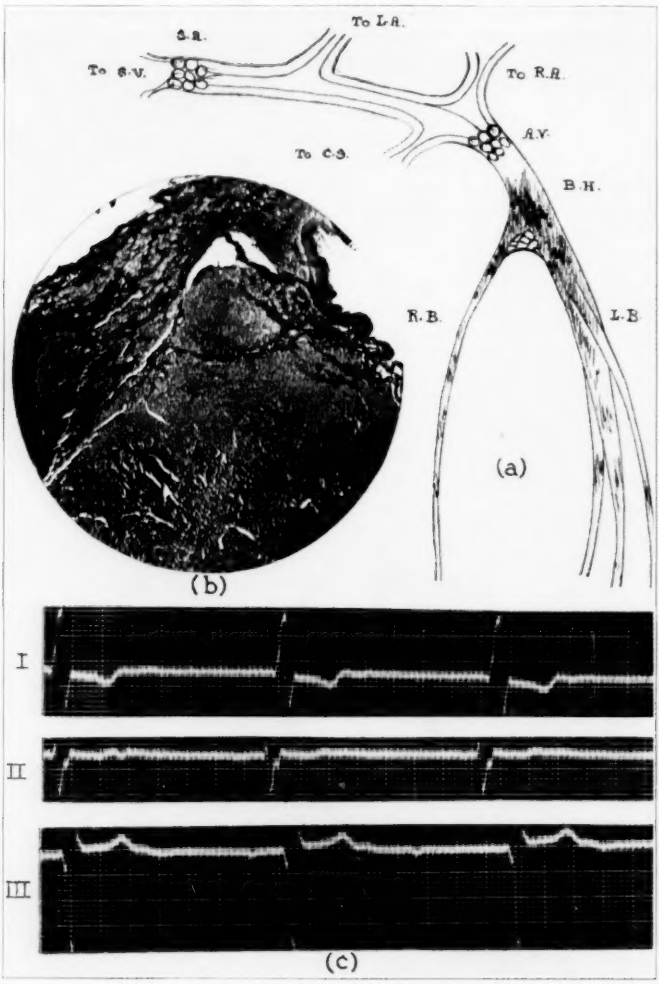

Fig. 5.—In *a* fibrosis, calcification and fatty changes affect the common bundle of His and both of its branches. *b* is a photomicrograph, showing the same. The fat cells are seen in the roughly triangular clear zone with faint subdivisions (reduced from × 16). *c* is an electrocardiographic tracing (three leads), showing evidence of a complete heart block in lead II. There is a left ventricular preponderance.

Microscopic Data (fig. 5*a* and *b*).—The essential pathologic changes were found in a section which included the interventricular septum with the membranous portion and the posterior wall of the right auricle.

In the uppermost portion of the septum, where it bordered the membranous part, there was a crescent-shaped area which was composed of large fat cells. Between the latter and the membranous portion proper, there was a triangular zone in which the muscle fibers were atrophic and had lost their striation. From the two pointed ends of the crescent, strands of a dense sclerotic scar tissue extended to the slightly thickened endocardium. On the right side, the muscle fibers were completely replaced by dense fibrous tissue and calcium concretions. On the left side, the changes were less extensive, but here too, in one area, the musculature was completely interrupted by the fibrosis.

The deeper portions of the right bundle branch was interspersed by dense fibrous strands which contained calcium concretions. On the left side, the changes were less intensive. Toward the apex of the heart, the scarring on both sides became less marked and finally disappeared.

The walls of the smaller arteries were markedly thickened due to hypertrophy of the muscle fibers and an increase of elastic tissue. The internal and external elastic membranes were thickened, the former showing a splitting in many instances. The intimas were unchanged and the lumens patent. The arterioles similarly showed a thickening of their walls. The precapillaries and capillaries were hugely distended and filled with blood.

Outside of the scarred areas the muscle fibers were hypertrophic, and a yellowish-brown pigment had accumulated about the nuclei.

Anatomic Diagnosis.—This was: complete fibrotic interruption of the bundle of His at the point of division; hypertrophy of the heart, especially the left ventricle, with marked dilatation of all the cardiac chambers; chronic passive congestion of the liver and spleen with fibrosis; ascites and anasarca of the lower extremities.

The enlarged heart (700 Gm.) without evidence of valvular or coronary changes, the increased blood pressure, 182 systolic and 64 diastolic, and the absence of pathologic changes in the kidneys speak for an essential hypertension. The histologic changes in the arteries, arterioles and capillaries, especially of the heart, bear out this diagnosis.

The etiology of essential hypertension is unknown, but it is suggested that the underlying pathogenesis is an increased tonus of the small arteries and the arterioles produced by some toxin, bacterial, metabolic or chemical. The toxin, while producing an increased tonus of the small arteries and the arterioles, causes a dilatation of the precapillaries and capillaries (Ricker [27] and Dietrich [28]). From a histologic standpoint, this is borne out in case 3 by the hypertrophy of the media of the small arteries and arterioles and the dilatation of the precapillaries and capillaries.

27. Ricker, G.: Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927.

28. Dietrich, A., and Nordmann, M.: Versuche zur hämorrhagischen Diathese, Verhandl. d. deutsch. path. Gesellsch. **25**:46, 1930.

With increasing doses of the noxa, there are a greater constriction of the small arteries and arterioles and a wider dilatation of the precapillaries and capillaries, which may lead to paresis of the smaller vessels (prestasis) or actual paralysis (stasis) (Ricker [27]). With such vascular phenomena, degenerative changes and even necrosis may result.

This vascular mechanism is apparently responsible for the pathologic changes described. As the picture is that of an advanced stage in which fatty, calcific and fibrotic changes are prominent, the changes embrace the bundle of His and its branches, because they are richly supplied with blood vessels.

INFLAMMATORY LESIONS OF THE CONDUCTIVE APPARATUS

The existence of myocarditis as an entity is much disputed. Undoubtedly, it exists, as inflammatory conditions of any organ may exist. Acute isolated myocarditis has been described by Mönckeberg,[29] Schmincke,[30] de la Chapelle and Graef,[31] Scott and Saphir [32] and many others. The majority of the reports, however, exclude the valvular lesions merely by gross inspection. That microscopic lesions do exist has been shown clearly by de Vecchi.[33] Whether the endocardial affectations precede or are concomitant with the myocardial involvement is sometimes difficult to determine, but the importance of these microscopic lesions should not be underestimated in the pathogenesis of myocarditis.

In case 4, an acute myocarditis was associated with micro-ulcerative endocarditis. Grossly, the valves appeared unchanged. It is possible that the endocarditis influenced the myocarditis. Unfortunately, an electrocardiographic record was not obtained in this case because the patient died shortly after entering the hospital. Although the slow pulse rate (from 30 to 40 per minute) does not necessarily spell heart block, it is interpreted as such because of the anatomic findings.

CASE 4.—*History.*—A white man, aged 42, was brought to the hospital markedly dyspneic, cyanotic and complaining of severe abdominal pain; he hiccuped

29. Mönckeberg, J. G.: Die Erkrankungen des Myokards und des spezifischen Muskelsystems, Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, pp. 356, 366, 387 and 435; Zur Einteilung und Anatomie des Adams-Stokes'schen Symptomenkomplexes, Beitr. z. path. Anat. u. z. allg. Path. **63**:77, 1916; Das spezifische Muskelsystems in Mensch Herzen, Ergebn. d. allg. Path. u. path. Anat. **19**:328, 1921.

30. Schmincke, N.: Isolierte akute, diffuse interstitielle Myokarditis, Deutsche med. Wchnschr. **47**:1047, 1921.

31. de la Chapelle, C. E., and Graef, I.: Acute Isolated Myocarditis, Arch. Int. Med. **47**:942 (June) 1931.

32. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, Am. Heart J. **5**:129, 1929.

33. de Vecchi, B.: The Endocarditic Process in Childhood, Arch. Path. **12**:49 (July) 1931.

at frequent intervals. His history was indefinite; he had had cramplike pains in his abdomen five days previously, following a gastric upset. The pains were less severe the following day, but recurred more severely and persisted. Vomiting, from three to four times daily, was associated with the pain, and a relative thought that it had been blood-tinged at one time. Together with the foregoing symptoms, dyspnea was marked.

The past history was irrelevant, the patient having enjoyed good health until the present illness.

Examination.—On physical examination his temperature was found to be 103.8 F. (rectal); the respiratory rate 32 per minute. The pulse was imperceptible at the wrist, but the carotids pulsated irregularly at a rate of from 30 to 40 per minute. The blood pressure could not be obtained.

The heart was slightly enlarged to the left, the apex being a little outside of the left nipple line. The tones were weak and irregular, and the rate was from

TABLE 4.—*Summary of Case 4*

	Diagnosis		
	Pathologic	Clinical	Electrocardiographic
Sino-auricular node....	No change	Coronary thrombosis with possible heart block or bleeding peptic ulcer	No tracing made as patient died 2 hours after entering hospital
Auricular fibrils.....	Few polymorphonuclear leukocytic infiltrations		
Atrioventricular node..	No change		
Common bundle of His	Acute inflammatory changes with hemorrhages		
Left branch.....	Destroyed by marked acute inflammatory changes and hemorrhages		
Right branch.....	Destroyed by moderate acute inflammatory changes and hemorrhages		
Arborizations.....	Slight granulocytic infiltrations and hemorrhages		
Comments.....	Micro-ulcerative endocarditis of aortic valve	Heart rate from 30 to 40 per minute	

30 to 40 per minute. The lung findings were entirely negative. The abdomen was distended, but there were no masses, tenderness or rigidity. Borborygmus was increased throughout. The skin was cold and clammy, and the reflexes were diminished.

The impression was that the patient had coronary thrombosis with possible heart block, but because of the history of bleeding and abdominal cramps, a bleeding ulcer was considered.

Although the patient gave the major portion of the history, his death occurred two hours after he entered the ward, so that no further study was possible.

Postmortem Examination (Dr. S. R. Rosenthal).—The body, weighing 142 pounds (64.4 Kg.) and being 162 cm. in length, was that of a strongly built Italian man, whose face was moderately cyanotic.

The heart weighed 325 Gm.; the left ventricle measured 15 mm., and the right ventricle, 2 mm. The myocardium was a deep purple brown and soft. The valves appeared normal grossly. In the region of the membranous portion of the interventricular septum, facing the left ventricle, there was an irregular subendothelial

extravasation of blood, extending for a distance of 2 cm. in diameter. A sagittal section of the interventricular septum revealed that the hemorrhage extended through the entire wall, for 1 cm. below the membranous portion of the septum.

The coronary arteries were thin-walled, and the intima was occasionally studded by a yellow plaque of 2 or 3 mm. The intima of the aorta was smooth.

The spleen weighed 140 Gm.; its consistency was soft, and the pulp was purple red mottled with pink red.

The remaining organs showed evidences of passive congestion. The gallbladder contained mulberry-shaped, light yellowish-green stones. The mucosa of the gallbladder was trabeculated and light yellow.

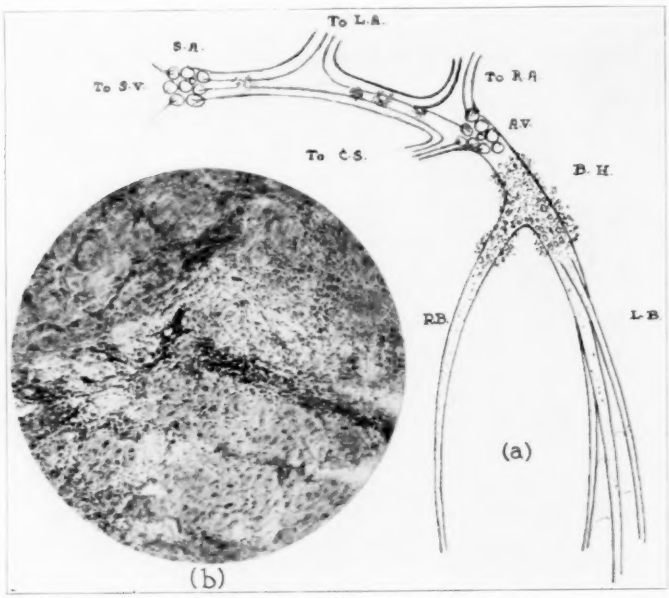

Fig. 6.—In *a* there are acute inflammatory exudate and hemorrhage in the region of the bundle of His. *b* is a photomicrograph in the region of the common bundle (reduced from × 150).

Microscopic Data (fig. 6*a-b*).—Interventricular Septum, Including the Posterior Aspect of the Right Auricle: Beginning in the lower third of the membranous portion of the septum on the right side and extending for 1 cm. into the apex of the muscular portion of the septum were extensive extravasations of blood which permeated beneath the endocardium of the left ventricle, and to a lesser extent the right ventricle. Marked polymorphonuclear leukocytic infiltrations were found about the extravasated blood, and granulocytes invaded both branches of the bundle just beneath the bifurcation. In the remaining portion of the muscular septum, the muscle fibers were hypertrophic; their cross-striations were indistinct, and about the nuclei were moderate amounts of a golden yellow pigment. Occasionally a small lake of blood was found about the vessels, which were surrounded by round cells and granulocytes.

In the right auricle were single small perivascular leukocytic infiltrations. The region of the atrioventricular and sino-auricular nodes appeared well preserved.

Aortic Valve (fig. 7): The aortic surface of the valve was covered by a cellular exudate, which was composed of several distinct layers. The proximal layer presented a diffuse zone of necrosis in which polymorphonuclear leukocytes were found in different stages of degeneration. The distal aspect was covered by a cellular layer of granulocytes, mononuclear cells and swollen fibrocytes. This layer was covered by proliferated endothelium. The necrosis and leukocytic infiltrations extended down into the sinus of Valsalva, but the covering productive layer became less and less distinct. On the ventricular aspect of the valve was also a thin layer of leukocytes and fibrin. In the fat tissue between the auricle and the root of the aorta were dense accumulations of polymorphonuclear leukocytes and mononuclear cells.

Anatomic Diagnosis.—This was: acute micro-ulcerative suppurative endocarditis of the aortic valve and suppurative hemorrhagic interstitial myocarditis, involving especially the bundle of His; acute tumor of the spleen; passive congestion of the myocardium and the liver; cholecystitis and cholelithiasis.

Similar to acute myocarditis, the etiology of subacute myocarditis is unknown. Because of the absence of Aschoff nodules and gross valvular lesions, it is not considered rheumatic and is thought by some to be primarily a myocardial inflammation (Roque and Levy,[34] Möncke-berg,[29] Krehl[35] and Boikan[36]). Other authors believe that it is tuberculotoxic (Massini[37]). The inadequate microscopic examinations of the heart valves again suggest them as possible sources of the infection.

The microscopic changes in the myocardium in case 5 are similar to those described in subacute myocarditis (Roque and Levy, Möncke-berg and Krehl) or myocarditis perniciosa (Boikan). This consists of a round cell and histiocytic infiltration which affects the ventricles more than the auricles and the interventricular septum more than the outer walls. No Aschoff nodules are present. Yet in case 5 a small, chronic, rheumatic lesion was found involving the posterior cusp of the mitral valve with a more recent verrucous deposit. It is possible to conceive that this lesion might have been microscopic in size, as in case 4, and overlooked grossly.

Case 5 represents a complete heart block as the result of a subacute inflammatory process involving the main bundle and both of its branches and a right ventricular preponderance as the result of a myomalacia of the apex of the left ventricle. The exudate also extended beneath the

34. Roque and Levy: Un cas de myocardite subaiguë primitive, Arch. d. mal. du cœur **7**:10, 1914.

35. Krehl, L.: Beitrag zur Kenntnis der idiopathischen Herzmuskelerkrankungen, Deutsches Arch. f. klin. Med. **48**:414, 1891.

36. Boikan, W. S.: Myocarditis perniciosa, Virchows Arch. f. path. Anat. **282**: 46, 1931.

37. Massini, R.: Ueber tuberkulöse Myokarditis, Schweiz. med. Wchnschr. **51**:1156, 1921.

endocardium of both ventricles, thus involving the arborizations. Yet there was no arborization block clinically. The short duration of the disease was probably insufficient to destroy completely the terminal ramifications of the bundle of His.

Fig. 7.—Micro-ulcerative endocarditis of the aortic valve (reduced from × 45).

Case 5.—*History.*—A white boy, aged 17 years, was well until four months before examination, when he began to experience epigastric fulness, which was not associated with meals and was not accompanied by nausea or vomiting. Soda or food did not relieve the distress. He had had numerous sore throats, and two months previously he had had a recurrence.

All of the foregoing symptoms were rather mild until four days before hospitalization, when the patient began to have chills and fever with marked diaphoresis. With rest he was slightly relieved, but on arising he became dizzy and weak and

had hot flashes. Three days following the onset, on getting out of bed, he fainted. Recovery was instantaneous. However, five and one-half hours later a convulsive seizure set in which recurred in two hours. He was rushed to the hospital, and in the interim had two more convulsions.

Previously, he had noticed sharp pains over his precordium, palpitation and dyspnea, but never convulsions. His previous illnesses included chickenpox, whooping cough and tonsillitis, as noted. Tonsillectomy, which was performed four years before hospitalization, did not abate the sore throats.

Examination.—The patient had endured from six to eight epileptiform attacks. These consisted of an aura of "feeling hot all over," rolling of the eyes and dilatation of the pupils, which did not react to light. There was a jerking of the head, followed first by tonic and then a few clonic twitchings of the lower extremities. The deep reflexes were increased during the attack, and there was involuntary urination.

The heart rate was irregular during this time. Immediately preceding an attack, the heart tones at the apex disappeared and the cardial pulse was imperceptible. These conditions lasted for from fifteen to thirty seconds. Then the apex tones began again, one or two at a time at first and then more frequently at the close of the seizure, but with absolute irregularity. This state continued until the next attack, which was heralded by a gradual loss of the apex beat until it became entirely absent. The attacks occurred every five or ten minutes for forty minutes and then stopped. The rhythm gradually became regular, or nearly so, and the rate varied from 48 to 52 per minute. The pulse was of the bigeminus type.

Examination of the heart some time after complete recovery from the attack revealed a moderate transverse enlargement. There were no murmurs, and the heart beat was regular and uniform, but feeble. The rate was 82 per minute.

The liver was slightly enlarged, and the entire abdomen was voluntarily rigid. Neurologic examination was entirely negative.

Urinalysis disclosed nothing; the Kahn reaction of the blood was negative; the Wassermann reaction of the spinal fluid was negative. The white blood count was 17,150, with 75 per cent polymorphonuclear leukocytes, 1 per cent eosinophils and 23 per cent lymphocytes.

An x-ray picture of the chest verified the transverse enlargement of the heart.

The electrocardiographic reading was as follows (Dr. H. J. Isaacs): ventricular rate, 50; auricular rate, 135; complete heart block; right ventricular preponderance; marked notching of the Q-R-S complexes (fig. 8 *c*).

The diagnosis was acute to subacute myocarditis with superimposed heart block and a Stokes-Adams syndrome.

Course.—While the patient was in the hospital he had numerous seizures, during which his heart rate would become low or absent, as described, but in the intervals his pulse was normal or elevated in rate, varying from 88 to 132 beats per minute. The pulse was irregular at times, but as a rule was regular and feeble. He continued to run an intermittent temperature (from 98 to 102 F. [rectal]). Terminally, dyspnea, orthopnea and cyanosis set in. The patient died one week after the onset of acute symptoms and four months after his first complaints.

Postmortem Examination (Dr. S. R. Rosenthal).—The body, weighing 135 pounds (61.2 Kg.) and being 171 cm. in length, was that of a strongly built boy, whose mucous membranes were pale. The skin of the neck and shoulders was discolored a deep purple red.

The heart weighed 500 Gm. The left ventricular wall was 15 mm. in thickness, and the right ventricular wall was 4 mm. The myocardium was a glossy, red

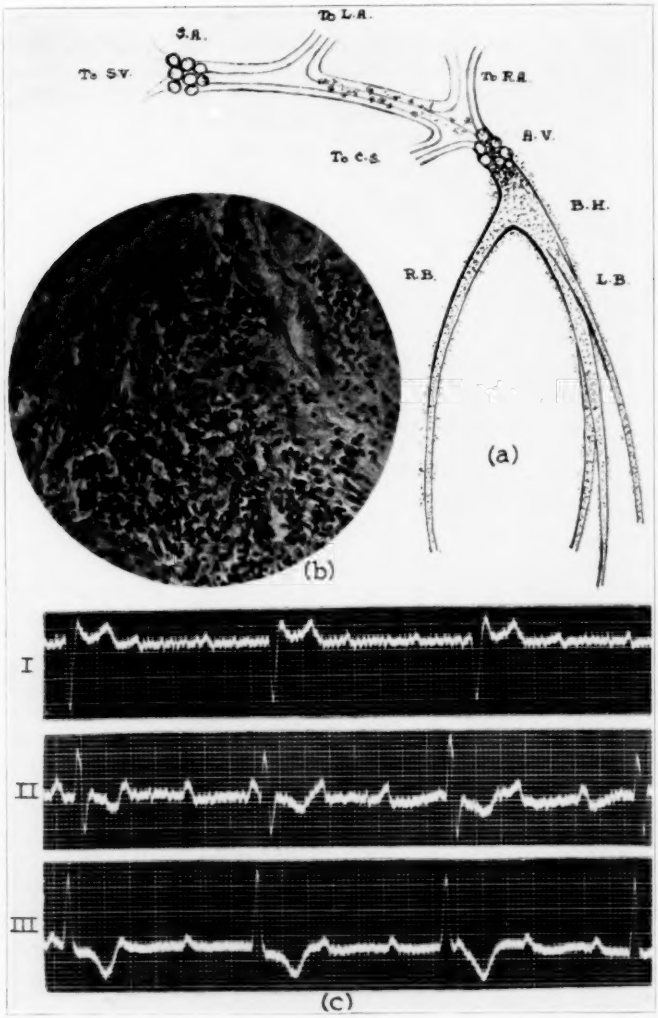

Fig. 8.—In *a* there is lymphocytic, histiocytic and granulocytic infiltration of the entire bundle of His and its branches. *b* is a photomicrograph of the region of the bundle of His (reduced from × 300). *c* is an electrocardiographic tracing (three leads), showing complete heart block.

brown mottled with tan. Its consistency was soft, especially near the apex, where the innermost portion of the myocardium of the left ventricle was pultaceous. A mural thrombus, measuring 4 by 2.5 by 2 cm., covered the softened area and was adherent to it. The endocardium of the remaining left ventricle was slightly thickened and pale gray; the trabeculae carneae were flattened. The circumference of the left ventricle was 110 mm., while the height was 90 mm. The right ventricle showed a moderate dilatation. The free margin of the posterior leaflet of the mitral valve was slightly thickened, and superimposed on this was a fine, granular deposit.

The coronary arteries were thin-walled and smooth. The aorta showed no gross changes.

TABLE 5.—*Summary of Case 5*

	Diagnosis		
	Pathologic	Clinical	Electrocardiographic
Sino-auricular node....	No change	Subacute myocarditis with superimposed heart block and Stokes-Adams syndrome	Complete heart block; right ventricular preponderance; marked notching of Q-R-S complexes
Auricular fibrils.....	Moderate round cell infiltration		
Atrioventricular node..	Interstitial infiltration of lymphocytes, monocytes and histiocytes		
Common bundle of His	Extravasation of blood with round cell and histiocytic infiltrations		
Left branch.....	Marked small round cell infiltrations; moderate number of histiocytes and polymorphonuclear leukocytes		
Right branch.....	Marked small round cell infiltrations; moderate number of histiocytes and polymorphonuclear leukocytes		
Arborizations.....	Marked infiltrations beneath endocardium of left and right ventricle of lymphocytes, histiocytes, and few granulocytes		
Comments.....	Fibroplastic deformity of the mitral valve with recent verrucous deposits		Myomalacia of left ventricle accounted for the right ventricular preponderance

The liver weighed 1,845 Gm.; there was a fine fibrinous exudate on its capsule, and in the parenchyma were small areas of central red atrophy. The spleen weighed 270 Gm., and its capsule was covered by a fine fibrinous exudate. The pulp was deep red and soft, and the follicles were prominent.

The remaining organs were congested and occasionally showed small petechial hemorrhages.

Microscopic Data.—Interventricular Cardiac Septum, Including the Posterior Wall of the Right Auricle (fig. 8*a* and *b*): In the region of the atrioventricular node, a well isolated group of muscle fibers, which had ample sarcoplasm, presented an interstitial infiltration of small round cells, a few granulocytes and histiocytes. Many of the specialized muscle fibers were shrunken, had pyknotic nuclei and in places were entirely replaced by the cellular infiltrations. The remainder of the auricle showed a moderate perivascular round cell infiltration and a loss of cross-striations of the muscle fibers.

In the membranous portion of the interventricular septum, beneath the endocardium bordering the right ventricle, was a moderate extravasation of blood. A few mononuclear cells, scattered in small foci, prevailed throughout.

The most prominent changes were found in the muscular portion of the interventricular septum. It was extensively infiltrated, especially in its superior aspect, by small round cells and to a lesser extent by granulocytes, especially eosinophilic, and swollen adventitial cells. The exudate appeared most pronounced between the muscle bundles, but in many instances invaded the muscle cells and replaced them. Beneath the endocardium of both ventricles, the cellular extravasations arranged themselves in sheets, but spared the endocardium. The latter was slightly thickened by edema and a proliferation of the lining cells.

The vessels were unusually dilated and toward the center of the septum were ruptured, and small extravasations of blood surrounded them.

By staining with the van Gieson method, no increase of fibrous tissue or scarring was noted in the muscular portion of the septum. In the region of the atrioventricular node, however, the muscle bundles were interspersed with fibrous strands that stained a deep red.

The elastica stain clearly demonstrated the marked dilatation of the vessels in the center of the septum, their ruptured internal elastic membranes and the escape of blood.

The Superior Portion of the Right Auricle Near the Superior Vena Cava: In the vicinity of the sino-auricular node was a wedge-shaped area beneath the endocardium, which was composed of large cells with ample sarcoplasm and deeply staining shrunken nuclei. Surrounding this node, for a short distance, the muscle bundles were infiltrated by small lymphocytes and fewer granulocytes. Although this exudate was most marked between the muscle fibers, there were also invasion and destruction of the muscle. On the whole, the invasion of the auricular musculature was negligible in comparison with the ventricular invasion.

Anatomic Diagnosis.—This was: subacute myocarditis with invasion of the atrioventricular node, the common bundle of His and both branches; heart block (clinical); myomalacia of the apex of the left ventricle with mural thrombus formation; focal epicardial fibrosis over the anterior aspect of the apex of the left ventricle; slight fibroplastic deformity of the posterior cusp of the mitral valve with recent verrucous endocarditis of this leaflet.

COMMENT

Excluding extracardiac lesions, the pathologic changes that may affect the conducting apparatus and lead to heart block are as follows:

Inflammatory.—Acute and Subacute: Notably in the course of diphtheria, endocarditis, pericarditis and nephritis, heart block may occur (Mönckeberg,[29] Schmincke,[30] Aschoff,[38] Gerhardt,[39] Sternberg,[40]

38. Aschoff, L.: Referat über die Herzstörungen in ihren Beziehungen zu den spezifischen Muskelsystemen des Herzens, Verhandl. d. deutsch. path. Gesellsch. **14**:3, 1910; Zur Frage der subendokardialen Blutungen, Virchows Arch. f. path. Anat. **213**:176, 1913.

39. Gerhardt, D.: Ueber Rückbildung des Adams-Stokes'schen Symptomenkomplexes, Deutsches Arch. f. klin. Med. **93**:485, 1908.

40. Sternberg, C.: Ueber Erkrankungen des Myokard, Wien. klin. Wchnschr. **41**:1045, 1928; Beiträge zur Pathologie des Atrioventrikularbündels, Verhandl. d. deutsch. path. Gesellsch. **14**:102, 1910.

Lasowsky,[41] Taussig,[42] Price and Mackenzie[43] and Rohmer[44]). The histologic picture is that of dense infiltrations of lymphocytes and polymorphonuclear leukocytes in the myocardium of both ventricles, especially the interventricular septum. The auricles are usually spared. The bundle of His and its branches are more frequently involved than the nodes. The sino-auricular node is rarely involved, while the atrioventricular node is relatively commonly affected (cases 4 and 5).

Chronic: Syphilis is the most common chronic inflammatory condition and may manifest itself as an interstitial myocarditis (Hill[5]) or actual gummas (Mönckeberg,[29] van den Bovenkamp,[45] T. Fahr[46] and Robinson[47]). Aneurysms interrupting the bundle or the atrioventricular node have been described by Roth[21] (case 1). A tuberculosis lesion involving the sino-auricular node has been described by Ceelen.[48]

Vascular.—Atherosclerosis: Sclerosis of the coronary artery may lead to fibrotic, calcific and fatty changes of the nodes, the bundle of His and the myocardium (Mönckeberg,[29] Engel,[49] Fleming and Kennedy,[50] Géraudel, Broden and Lereboullet[51] and Barnes and Yater[52]). However, complete intersection of the bundle must exist before clinical signs of block will be evident (case 2).

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41. Lasowsky, J. M.: Normale und pathologische Histologie der Herzganglien der Menschen, Virchows Arch. f. path. Anat. **279**:464, 1931.

42. Taussig, H. B.: A Case of Bundle Branch Block Confirmed by Pathological Study, Bull. Johns Hopkins Hosp. **45**:40, 1929.

43. Price, F. W., and Mackenzie, I.: Auricular Fibrillation and Heart Block in Diphtheria, Heart **3**:233, 1912.

44. Rohmer, P.: Neuere Untersuchungen über den Diphtherieherztod, Jahrb. f. Kinderh. **76**:361, 1912.

45. van den Bovenkamp, G. J.: A Case of Total Heart-Block from a Gumma, Nederl. tijdschr. v. geneesk. **68**:1502, 1924.

46. Fahr, T.: Anatomische Beiträge zur Frage der Herzinsuffizienz, Verhandl. d. deutsch. path. Gesellesch. **14**:105, 1910.

47. Robinson, G. C.: Gumma of the Heart from a Case Presenting the Symptoms of Adams-Stokes' Disease, Bull. Ayer Clin. Lab. Pennsylvania Hosp. **4**:1, 1907.

48. Ceelen, W.: Das Reizleitungssystem des Herzens, Berl. klin. Wchnschr. **56**:509, 1919.

49. Engel, Irmgard: Beiträge zur normalen und pathologischen Histologie des Atrioventrikularbündels, Beitr. z. path. Anat. u. z. allg. Path. **48**:499, 1910.

50. Fleming, G. B., and Kennedy, A. M.: A Case of Complete Heart-Block in Diphtheria, with an Account of the Post-Mortem Findings, Heart **2**:77, 1910.

51. Géraudel, E.; Brodin, P. L., and Lereboullet, J.: Étude d'un cas de syndrome d'Adams-Stokes mortel: Nécrose transverse du ventriculo-necteur par endartérite sténosante de son artère, Arch. d. mal. du cœur **22**:1, 1929.

52. Barnes, A. R., and Yater, W. M.: Paroxysmal Tachycardia and Alternating Incomplete Right and Left Bundle-Branch Block with Fibrosis of the Myocardium, M. Clin. North America **12**:1603, 1929.

Thrombosis: Thrombosis or embolism of the coronary arteries with infarction of the interventricular septum may lead to a complete heart block (Brinck, Miszke and Schöne [24] and case 2).

Endarteritis: Endarteritis of the vessels supplying the bundle of His may lead to a fibrosis or necrosis of the same (Géraudel and Gautier [53]).

Hypertension: In the literature, no mention is made of the mechanism by which heart block results in a hypertensive heart. Prestasis and stasis of the precapillaries and capillaries as a result of an increased tonus of the smallest arteries and arterioles lead to degenerative changes of the supplied parenchyma. Because the bundle of His is so richly supplied with blood vessels, the former becomes especially prone to vascular alterations (case 3).

Toxic.—Drugs: Overdoses of digitalis have been repeatedly reported as producing heart block (Aschoff,[38] Mönckeberg [29] and Cohn and Lewis [16]). This is explained by Aschoff on the basis of hemorrhages that occur subendocardially and within the bundle of His as a result of violent contractions of a damaged myocardium.

Bacterial Toxins: In the early stages of diphtheria (Mönckeberg,[29] Butler and Levine [54] and Aschoff [38]), in tetanus (Ribbert [55]) and in intestinal toxemias (Taylor [56]), extensive hemorrhage may be found in the interventricular septum. This is a result of the severe degenerative changes in the myocardium, which ruptures as a result of the contractions (Berblinger,[57] Amenomiya,[58] Rohmer,[44] Magnus-Alsleben [59] and Fleming and Kennedy [50]). Direct vascular damage may also be responsible for extravasations of the blood or for myolysis (Mönckeberg [29]).

Neoplastic.—Primary sarcomas of the heart leading to block are exceedingly rare. A lymphangio-endothelioma of the atrioventricular

53. Géraudel, E., and Gautier, C.: Syndrome d'Adams-Stokes par nécrose transverse du ventriculo-necteur consécutive à une endardérite oblitérante de son artère, Ann. d'anat. path. **8**:339, 1931.

54. Butler, S., and Levine, S. A.: Diphtheria as Cause of Late Heart-Block, Am. Heart J. **5**:592, 1930.

55. Ribbert, H.: Ueber die subendokardialen Blutungen im Bereiche des Atrioventrikularbündels, Deutsche med. Wchnschr. **41**:211, 1915.

56. Taylor, F. L.: A Case of Transient Heart Block Due to Intestinal Toxemia, J. A. M. A. **50**:1246 (April 18) 1908.

57. Berblinger, W.: Ueber die subendokardialen Blutungen, die Beziehungen zwischen Blutung und Degeneration der Herzmuskelfasern, Centralbl. f. allg. Path. u. path. Anat. **28**:1 1917.

58. Amenomiya, R.: Ueber das Atrioventrikularbündel des Herzens bei Diphtherie, Virchows Arch. f. path. Anat. **202**:107, 1910.

59. Magnus-Alsleben, E.: Zur Kenntnis der vorübergehenden Ueberleitungsstörungen des Herzens, Ztschr. f. klin. Med. **69**:82, 1909.

node was described by Lloyd,[60] as well as by Armstrong and Mönckeberg.[61] A fibroxanthosarcoma was described by Dietrich[62] and a rhabdomyoma by Bundschuh[63] and Mönckeberg.[29] Metastatic carcinomas have been described by Mönckeberg.

Congenital.—Several cases have been reported of complete heart block as a result of congenital defects of the interventricular septum, especially the membranous portion, which is the last to fuse (Brandenburg[64]).

Traumatic.—An injury in the region of the precordium, producing a complete heart block which lasted over several years, was reported by Coffen.[65]

Senile.—In elderly people, degenerative changes of the conducting system are common, but block is rare (Bönniger and Mönckeberg[66]). In heart diseases of all types, Sternberg[40] found anatomic lesions in the bundle in 70 per cent. Brown atrophy with fibrosis and calcific changes producing block has been described by Lasowsky.[41]

Functional.—This type of block cannot be accepted as a true entity, for in such cases that have been reported either no postmortem findings were given or thorough histologic studies were wanting (Hume[67] and Mollard, Dumas and Rebattu[68]). Gerhardt's[39] observation is illuminating in this regard. His patient had several attacks of heart block in the course of rheumatic fever. The attacks lasted from two to three weeks at a time and were associated with an Adams-Stokes syndrome. The

60. Lloyd, P. C.: Heart Block Due to Primary Lymphangio-Endothelioma of the Atrio-Ventricular Node, Bull. Johns Hopkins Hosp. **44**:149, 1929.

61. Armstrong, H., and Mönckeberg, J. G.: Herzblock, bedingt durch primären Herztumor bei einen 5 jährigen Kinde, Deutsches Arch. f. klin. Med. **102**: 144, 1911.

62. Dietrich, A.: Ueber ein Fibro-xanthosarcoma mit eigenartiger Ausbreitung und über eine Vena cava superior sinistra bei dem gleichen Fall, Virchows Arch. f. path. Anat. **212**:119, 1912.

63. Bundschuh, E.: Ein weiterer Fall von tuberöser Sklerose des Gehirns mit Tumoren der Dura mater, des Herzens und der Nieren, Beitr. z. path. Anat. u. z. allg. Path. **54**:278, 1912.

64. Brandenburg, K.: Dauernder vollständiger Vorkammer-Kammerblock bei einem 4 jährigen Knaben—angeborener Herzfehler, subaortaler Septumdefekt, Med. Klin. **25**:1464, 1929.

65. Coffen, T. H.: Complete Heart-Block of Seven Years' Duration in a Child Resulting from an Injury, Am. Heart J. **5**:667, 1930.

66. Bönniger, M., and Mönckeberg, J. G.: Untersuchungen über das Atrioventrikularbündel des menschlichen Herzens, Deutsche med. Wchnschr. **34**:2293, 1908.

67. Hume, W. E.: A Case of Heart-Block in Which There Was No Pathological Lesion of the Connecting Muscular System, Heart **5**:149, 1914.

68. Mollard, J.; Dumas, A., and Rebattu, J.: Syndrome de Stokes-Adams, sans lésion du faisceau de His, Arch. d. mal. du cœur **4**:298, 1911.

patient recovered clinically, but died a few months later of typhoid fever. Histologic studies of the heart disclosed round cell infiltrations and sclerosis of the vessels within the bundle.

SUMMARY AND CONCLUSIONS

Although single pathologic cases cannot unconditionally confirm or refute experimental results, their importance is singular when they reduplicate experimental conditions. The aneurysm of the sinus of Valsalva, involving only the left branch of the bundle of His, and its prediction by the dextrocardiogram strongly support the original work of Eppinger Rothberger[9] and question the interpretations of Wilson, Macleod and Barker.[13] Strengthening this doubt are the preponderance anatomically of left over right ventricular hypertrophy and its verification by the electrocardiogram.

Arborization block per se cannot be considered as a distinct entity and when present is associated with an interruption of one or both of the main branches of the bundle. Coronary sclerosis with infarction of the interventricular septum or chronic myocarditis with marked scarring may produce the aforementioned lesion. Acute inflammations will not produce an arborization block, because the destruction of the arborizations is probably not complete.

Acute or subacute myocarditis may lead to heart block by invasion of the atrioventricular node, the bundle of His or its branches. Endocarditic lesions were found in the two cases of myocarditis reported, one being microscopic in size and the other focal and small. Because of the cases reported in the literature as myocarditis of unknown origin, in which few or no microscopic studies were made, it is suggested that the endocarditic lesions may have been microscopic and overlooked.

In a case of essential hypertension with heart block, the mechanism by which the degenerative changes took place in the bundle of His is explained by an increased tonicity of the small arteries and the arterioles and prestasis and stasis in the precapillaries and capillaries.

The various processes producing heart block, as deducted from the five cases reported and the literature, are presented.

STENOSIS OF THE SUPERIOR VENA CAVA DUE TO MEDIASTINAL TUBERCULOSIS

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Obstruction of the superior vena cava is the cause of the outstanding symptoms in many cases of mediastinal pathologic conditions. However, isolated stenosis of this vessel is distinctly rare.

Interference with the return flow of blood to the heart through the superior vena cava may arise from a wide variety of conditions in the mediastinum or in the vessel itself.

Of these causes, aneurysm,[1] almost universally of the aorta, is the most common. This lesion may compress and thereby result in slow partial mechanical obstruction of the superior vena cava and give rise to a train of symptoms due to this compression and compression of other mediastinal structures, such as the recurrent laryngeal nerves, trachea and esophagus. On the other hand, an aneurysm of the aorta may perforate into the vein, producing sudden functional stenosis of the vena cava as a result of the tremendous head pressure opposing the returning venous blood.

Mediastinal tumors are a common cause of superior caval obstruction, and present symptoms of this condition plus symptoms of compression of the other mediastinal structures. In this group are primary mediastinal tumors arising from the thymus,[2] substernal nodular goiter, carcinoma of a substernal thyroid and fibroma[3] and sarcoma of the mediastinum.

Metastasis or extension of a tumor into the mediastinum may give rise to caval obstruction. By far the most common tumors in this group are the bronchogenic carcinomas,[4] which are increasing in frequency.

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1. Packard, M., and Wechsler, H. F.: Am. Heart J. **6**:281, 1930.

2. Brannan, D.: Carcinoma of the Thymus and Occlusion of the Superior Vena Cava, Arch. Path. & Lab. Med. **1**:569 (April) 1926. Foot, N. C.: Am. J. Path. **2**:33, 1926.

3. Pastau: Virchows Arch. f. path. Anat. **34**:236, 1865.

4. Brown, A. L.: Complete Occlusion of the Superior Vena Cava by Primary Carcinoma of the Lung, Arch. Surg. **21**:959 (Dec.) 1930. Dana, H. W., and McIntosh, R.: Am. J. M. Sc. **163**:411, 1922.

Hodgkin's disease [5] and the leukemias occasionally cause symptoms of venous obstruction in this region.

Mediastinitis is liable to give rise to isolated vena caval obstruction by pressure, constriction of the vein by scar tissue, secondary phlebitis and even endophlebitis. Here tuberculosis is the most common, either as localized tuberculosis of the mediastinal lymph glands or as extension from a tuberculous lesion in the lung. Syphilis of the mediastinum,[6] ecchinococcus disease in the mediastinum, extension of rheumatic pericarditis and nonspecific mediastinitis with secondary arteriovenous aneurysm [7] have been described as causes.

Thrombosis of the primary superior vena cava, following influenza,[8] due to secondary phlebitis [9] or by extension of thrombi from tributary veins has been observed.

The symptoms arising from superior vena caval obstruction are the result of venous stasis in the parts drained and attempts to compensate for it. The superior vena cava drains the head and neck, the upper extremities and the thoracic wall to the level of from the fourth to the sixth ribs. Occlusion of the vein results in variable degrees of edema and cyanosis of these parts. The attempt to compensate results in dilatation of the tributary vessels with reversal of flow in those leading ultimately to the inferior vena cava.

It is noteworthy that the edema is most prominent in the head and neck and least prominent in the arms. This is probably the result of the auxiliary effect of the voluntary muscles in propelling the blood through the veins. Further, the edema and all other symptoms are accentuated by changes in posture that lower the upper half of the body in relation to the lower half, thus preventing gravity from aiding the return flow of blood to the heart. The subjective symptoms of superior caval stenosis are due chiefly to the marked passive congestion of the brain.

The clinical picture is a varying blend of venous obstruction and distention of the collateral circulation, depending on the rapidity of development and the degree of stenosis obtaining, and is more or less modified and often completely obscured by the concomitant effects of pressure on other mediastinal structures.

The picture seen in pure superior caval stenosis may be acute or chronic, the latter varying in degree.

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5. Osler, W.: Bull. Johns Hopkins Hosp. **14**:169, 1903.
6. Fraenkel: Deutsche med. Wchnschr. **17**:1378, 1891.
7. Chiovenda, M.: Arch. ital. di anat. e istol. pat. **1**:409, 1930.
8. Strauss, A.: Schweiz. med. Wchnschr. **59**:1410, 1929.
9. Perla, D., and Seligman, B.: Diffuse, Obliterating Endarteritis of Unknown Etiology: An Instance with Obliteration of the Inferior Vena Cava, Arch. Path. **7**:55 (Jan.) 1929.

Thus the functional stenosis resulting from the sudden overwhelming head pressure encountered by the venous blood when an aneurysm perforates into the superior vena cava gives rise to a dramatic, suddenly developing cyanosis of the upper half of the body, sharply demarcated at the level of the same area. Engorgement is especially prominent in the large veins, such as the jugular veins, but is also to be seen in the veins of the conjunctiva and eyegrounds. Edema of the conjunctiva with suffusion and papilledema are present. Subjectively dyspnea and orthopnea develop with almost explosive violence. Death usually intervenes early as the result of cerebral edema and congestion or of the primary pathologic process.

Gradually developing superior caval obstruction may result from any of the causes mentioned, and gives rise to a more or less insidiously developing train of symptoms which is toned down by the development of the collateral circulation. Thus the cyanosis is moderate, most pronounced in or limited to the head and neck or seen only in the mucous membranes of the mouth and conjunctiva. The edema is variable and limited to the head and neck; associated with suffusion, it is usually present in the conjunctiva. Engorgement of the cervical veins is pronounced, and, with the associated edema of the neck, gives rise to an increasing collar size. The superficial collateral veins are prominent, especially about the costal margins and to a lesser extent over the upper part of the abdomen and the upper section of the thorax. Polycythemia has been reported as occurring in the upper half of the body and later becoming generalized.[10] A similar phenomenon has been reported in the lower half of the body in cases of obstruction in the inferior vena cava.[11]

Subjectively the symptoms are dyspnea, orthopnea, dizziness, fulness in the head and constant sleepiness.

Obstruction to the flow of blood through the superior vena cava is not fatal per se, except when the onset is acute. This is attested to by one case of thirty years' duration that has been reported.[12] Death is the result of the underlying or associated pathologic conditions. In the rare long-standing cases all symptoms are slight, and the collateral circulation is abundant. However, the reserve is minimal, so that exertion will induce the symptoms even to an alarming degree.

REPORT OF A CASE

A white man, aged 42, an ex-prizefighter, was first seen on Feb. 5, 1931. He complained of dizziness, dyspnea, orthopnea, swelling of the face and neck and sleepiness. He had been well until the summer of 1930, when he noted dyspnea

10. Reckzeh: Ztschr. f. klin. Med. **57**:215, 1905. Abramson: California State M. J. **10**:14, 1912.

11. Tumen, H. J.: Am. J. Obst. & Gynec. **20**:417, 1930.

12. Claverie, G. E.: Thèse de Paris, no. 4, 1858.

on exertion, dizziness, orthopnea and drowsiness. At about the same time his face and neck began to swell and his collar size to increase. The symptoms were slowly progressive and were accentuated on exertion or stooping, and during the following months the swelling of the face and neck fluctuated in degree, depending on the physical activity of the patient. In about December, 1930, choking spells and extreme orthopnea disturbed him at night, and watering of the eyes became almost constant. A slight, rather insignificant cough had developed, and he lost about 6 pounds (2.7 Kg.).

The patient was well nourished, exceptionally well developed, short and stocky. The face and neck were definitely edematous and dusky; the lips were slightly cyanotic, and the conjunctivae were injected and edematous. The jugular veins were distended, and prominent varices encircled the costal margin.

Slight widening of the upper mediastinal dulness was noted on percussion. The blood pressure was 128 systolic and 78 diastolic in both arms. Laboratory examination revealed 10.5 Gm. of hemoglobin (Newcomer), 4,560,000 red blood cells and 5,350 white blood cells, with 40 per cent lymphocytes. The Wasser-

Fig. 1.—Photograph of the patient one and one-half years after the onset of stenosis of the superior vena cava. Edema is noted most prominently about the eyelids and neck but is nowhere very marked.

mann and Kahn tests were negative; the chemical examination of the blood gave normal results, and the urine was normal.

Roentgenograms and fluoroscopic examination revealed a slightly widened upper mediastinal shadow, which was interpreted as a tumor; no evidence of aneurysm was found.

Deep roentgenotherapy caused no change in the clinical findings during the following months. However, the hemoglobin was increased to 16.5 Gm. (Newcomer), and the red blood cell count to 5,480,000. The patient was observed until November, 1931, when he began to complain of increase in dyspnea, although objectively little change had occurred. The cause of the obstruction was thought to be a benign tumor, and in view of the hopeless outlook mediastinal exploration was undertaken by Dr. Lindon Seed.

Tremendously dilated superficial veins were encountered when the skin was incised. The right internal mammary vein was found to be about 8 mm. in diameter; when it was opened a stream of blood was thrown 20 cm. from the upper end. The mediastinum was widely exposed, but no tumor could be demon-

strated. The superior vena cava was distended, blue and thick-walled. The wound was closed, and the patient returned to bed apparently in good condition. On the following day the edema of the head and neck was increased, the arms were edematous, and cyanosis and dyspnea were pronounced. Respirations became rapidly more labored and the edema and cyanosis more pronounced, and the patient died on the second day after operation.

At autopsy the superficial, internal mammary, azygos and superior epigastric veins were found to be markedly dilated. A cartilaginous, rather poorly defined mediastinal mass was found adherent to the lung and encircling the superior vena

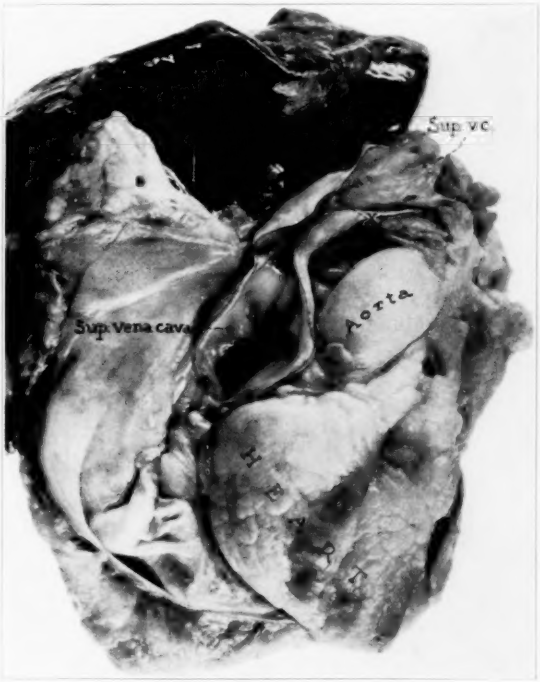

Fig. 2.—Stenosis of the superior vena cava. *X* indicates a dense valvelike flap completing the stenosis. The arrow indicates the passage, 2 mm. in diameter, that remains.

cava about 4 cm. above the right auricle. When the vessel was opened, its lumen in this region was demonstrated to be 2 mm. in diameter; the wall was thickened to 7 mm. by dense cartilaginous connective tissue, and the center of the encircling mass was made up of cheesy, necrotic material of the shape and appearance of a broken-down lymph gland. Above the point of stenosis the vessel was dilated moderately. The remaining organs were free from demonstrable pathologic conditions.

Microscopic sections through the area of stenosis displayed a central area of caseation necrosis. About this was a dense, hyalinized connective tissue stroma which was the seat of a diffuse and focal infiltration of lymphoid and epithelioid cells, fibroblasts, a few Langhans giant cells and occasional macrophages. No tubercle bacilli could be identified in sections stained by the Ziehl-Neelsen method. However, macrophages containing a few acid-fast granules of varying sizes were noted.

In view of the caseation necrosis and the location and the presence of the microscopic features described, in the absence of syphilitic features, either gross or microscopic, a diagnosis of chronic fibrocaseous tuberculosis of a mediastinal lymph gland was made. Death had resulted from the destruction of a considerable part of the collateral circulation in the absence of an appreciable circulatory reserve. The stenosis of the superior vena cava making this collateral circulation necessary had resulted from the extension of caseous lymph gland tuberculosis of the mediastinum with a marked desmoplastic reaction to involve the superior vena cava.

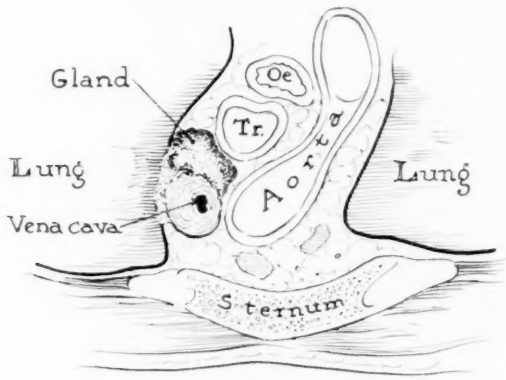

Fig. 3.—Diagrammatic sketch indicating the level of the stenosis and the relation of the caseous lymph glands to the vena cava and the lung.

COMMENT

This case illustrates the clinical picture of a chronic, rather slowly developing stenosis of the superior vena cava with terminal, rather acute obstruction. The complaints of dyspnea and orthopnea were dependent on the cerebral passive congestion with the concomitant increase in carbon dioxide in the cerebral circulation, resulting in respiratory stimulation. The drowsiness and probably the dizziness were caused by impaired cerebral circulation, with the resultant lowering of the metabolic possibilities of the vital centers. The limitation of the edema to the head and neck until the collateral circulation was suddenly reduced is explainable by the aid given the venous return by the skeletal muscles, while the effect of gravity in this regard explains the aggravation of the symptoms on stooping. The lack of reserve potentialities

in the venous return from the upper half of the body explains the aggravation of symptoms on exertion and the acute exacerbation of symptoms and death following the removal of part of the collateral circulation (right internal mammary vein).

Another phase of this case must be emphasized, namely, the etiology of the caval stenosis. Mediastinal tuberculosis in adults without demonstrable lesions or with only an old healed primary lesion in the pulmonary parenchyma is explainable on the basis of reactivation of the tracheobronchial lymph gland infection of the primary complex. It accounts for some of the pulmonary tuberculosis of adults, but offers almost insurmountable diagnostic difficulties when the pulmonary involvement is slight or absent.

The writer has encountered mediastinal tuberculosis giving rise to a cold abscess of the mediastinum with toxic nephrosis and finally extension into the pericardial sac to give rise to tuberculous pericarditis, or breaking into the general circulation and giving rise to miliary tuberculosis of the spleen, liver and kidneys with terminal pulmonary miliary tuberculosis. Instances of similar involvement of the esophagus [13] with traction diverticula, hemorrhage with sudden death [14] or tracheoesophageal fistula resulting are reported in the literature.

The roentgen findings in mediastinal tuberculosis are negative or at times misleading unless the glandular involvement is marginal and discrete or the seat of calcium infiltrations.[15] Therefore, mediastinal tuberculosis must be thought of as a possibility in obscure cases of mediastinal pathologic conditions and as the source of miliary tuberculosis or its clinical picture.

SUMMARY

1. The symptoms of vena caval obstruction are due to venous congestion and edema, are modified according to the degree of collateral circulation obtaining and are confused or obscured by other symptoms arising directly or indirectly from the underlying pathologic condition.

2. A case of tuberculosis of the tracheobronchial lymph glands causing superior caval stenosis is described.

3. The importance of mediastinal tuberculosis as the cause of a variety of clinical pictures is indicated.

2753 W. North Avenue.

13. Smellie, J. M.: Brit. J. Child. Dis. **20**:110, 1925.

14. Callis, H. A.: Am. J. Clin. Path. **1**:51, 1931.

15. McPhedan, F. M.: Am. J. M. Sc. **173**:245, 1927. Kornblum, K., and Cooper, D. A.: Am. J. Roentgenol. **23**:276, 1930.

COMBINED ACTIONS OF QUINIDINE AND DIGITALIS ON THE HEART

AN EXPERIMENTAL STUDY

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INTRODUCTION

Pharmacologic studies of the combined actions of digitalis and quinidine derive interest largely from the fact that while the two drugs possess some actions in common, they produce, with reference to certain other phenomena, diametrically opposite effects. Such studies have a direct practical bearing as well, because the two drugs are used together widely, especially in the treatment of patients with auricular fibrillation. Many of the clinical observations on quinidine have been made in digitalized patients. In these the fact that the heart may have been fully under the influence of digitalis frequently receives only casual mention or is even overlooked, and the appearance of toxic effects is ascribed to the action of quinidine alone, although some of these effects are never seen in normal animals after comparable doses of quinidine.

Experimental studies of the combined action of the two drugs in animals have not been very comprehensive, and investigations of their combined use in man have not gone materially beyond their actions on the fibrillating auricle. In view of the complexity of the actions of both quinidine and digitalis when used alone, and the variations in the effects in different species and with different doses, it becomes necessary to exercise extreme caution in drawing clinical inferences from the limited experimental results, these having been obtained in most instances under highly artificial conditions (morphine, ether or chlorbutanol anesthesia, thorax open, blood pressure low, massive doses of the drug).

The present investigation was undertaken to study one phase of the problem electrocardiographically in the normal unanesthetized dog. As quinidine is known to abolish various ectopic rhythms—auricular flutter

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and fibrillation, ventricular premature contractions [1] and ventricular tachycardia [2]—attention was directed chiefly to the effect of quinidine in the presence of an ectopic rhythm that is induced by digitalis most consistently, namely, ventricular tachycardia.

Rather striking results have been obtained. They show that quinidine and digitalis together produce effects that are almost never seen with either of the drugs alone under the same experimental conditions; that in the heart poisoned by digitalis, quinidine under some conditions may exert an apparently favorable influence and temporarily abolish the toxic rhythms induced by digitalis, while with a change in the conditions, it may provoke serious reactions that may even prove fatal in doses that are never fatal in the normal undigitalized animal and that are comparable to those well within the range of therapeutic doses for man.

The details of these experiments and their interpretation form the subject of the present report.

EXPERIMENTAL WORK

Sixteen experiments were carried out on eleven dogs. Three of the normal animals had been used from two to six days previously for the study of the action of quinidine alone, and serve to compare the effects of quinidine before and after digitalis in the same animal. The experimental procedure was essentially similar to that in the previous study.[3] Only such animals were selected as would remain perfectly quiet without restraint while the electrocardiographic tracings were taken and while the injections were being made. Three animals (five experiments) were vagotomized, the vagi being severed in the neck during light ether anesthesia. In these at least two hours elapsed before any injections were made, in order to allow for recovery from the anesthesia.

The cardiac changes were studied by means of electrocardiographic tracings, lead II only being used. Control records were made before any drug was given. After the animal was digitalized, tracings were taken at intervals to determine the changes in rhythm and the permanence of the desired ectopic rhythm. When the quinidine was given, a fairly uniform procedure was followed, the tracing being taken continuously before, during and for varying periods after the injection. In some the continuous tracings represented periods as long as four minutes. Between injections shorter tracings were taken at intervals varying from ten to fifteen minutes, but the galvanometer string was

1. Otto, H. L., and Gold, H.: Persistent Premature Contractions, Arch. Int. Med. **38**:186 (Aug.) 1926.

2. Levine, S. A., and Fulton, N. M.: The Effect of Quinidine Sulphate on Ventricular Tachycardia, J. A. M. A. **92**:1162 (April 16) 1929.

3. Gold, H., and Modell, W.: The Action of Quinidine on the Heart in the Normal Unanesthetized Dog, J. Pharmacol. & Exper. Therap., to be published.

observed almost continuously, and if any changes took place additional tracings were taken. In this way it was possible to record the immediate as well as the later effects of quinidine and also to determine the duration of the effects. From nine to thirty electrocardiograms of varying length were taken in the course of each experiment.

A tincture of digitalis (the alcohol evaporated off with moderate heat) was injected intravenously in total doses varying from 0.5 to 1.5 cat units per kilogram [4] given in fractional doses. It was necessary to give such large doses of digitalis because with the lesser degrees of poisoning the ventricular tachycardia tends to be paroxysmal, disappearing with changes in respiration or slight movement.[5] Quinidine sulphate was used in a 1 per cent solution made up in physiologic solution of sodium chloride. It was also injected intravenously in single doses varying from 1 to 16 mg. per kilogram,[4] and in total doses ranging from 2 to 47 mg.

In one animal an attempt was made to study the effects of quinidine by intramuscular injection. The results were duplicated in some of the experiments after the intravenous injections, a ventricular tachycardia disappearing about fifteen minutes after a dose of 10 mg. These injections, however, were painful and since the delay in the onset of changes introduced uncertainties into the interpretation of the results, intramuscular injections were not continued in other experiments.

Abridged protocols of the experiments are given in table 1. Only significant tracings are included. Time is represented in minutes and seconds from the beginning of the experiment. The period of the injection was recorded on the tracings, and the time stated in the table signifies the completion of the injection which, depending on the size of the dose, varied from about five to twenty-five seconds. Ventricular rates were determined from a count in from six to twelve second strips. In the presence of ventricular tachycardia, the P waves were often obscured in the Q-R-S groups, which made the determination of the auricular rate often impossible: hence only in those cases in which a few successive P waves appeared in the records was the sinus rate ascertained. Figures for the P-R intervals, whenever possible, represent the average of ten readings.

RESULTS

The injection of quinidine in dogs in which digitalis has produced a ventricular tachycardia results in a variety of changes depending on individual differences in the animal, the intensity of the digitalis poisoning and the doses of quinidine. It will not be feasible to discuss all the

4. All doses were given in milligrams per kilogram, but for the sake of brevity "per kilogram" will not be repeated throughout the paper.

5. Gold, H.; Lieberson, A., and Gelfand, B.: Mechanism of Production of Subauricular Beats by Digitalis Bodies, Arch. Int. Med. **48**:262 (Aug.) 1931.

TABLE 1.—*Abridged Protocols of the Experiments*

Time	Tracing	Rate: Auricle	Rate: Ventricle	P-R Interval	Comment
Experiment M					Digitalis at 46 and 79 minutes
96′	8a	...	170	....	Ventricular tachycardia
96′ 2″	....	...	...	....	Quinidine 2 mg.
96′10″	8c	...	185	....	Ventricular tachycardia
98′30″	8d	136	160	....	Ventricular tachycardia
102′	9	...	180	....	Ventricular tachycardia
224′	....	...	...	....	Vomited
230′	13a	...	230	....	Ventricular tachycardia
230′ 2″	....	...	...	....	Quinidine 1 mg.
230′45″	13c	...	170	....	Ventricular tachycardia
Experiment N					Digitalis at 14, 226 and 232 minutes
236′15″	10a	...	160	....	Ventricular tachycardia
236′30″	....	...	...	....	Quinidine 5 mg.
236′40″	10b	A*	125-A	....	Ventricular tachycardia, followed by asystole for 0.8 second
237′30″	10c	150	150	0.14	Sinus rhythm, lasting about 11 minutes with rate up to 180
262′30″	14a	190	190	....	Ventricular tachycardia
263′	....	...	...	....	Quinidine 5 mg.
263′30″	14b	190	160	....	Ventricular tachycardia
273′	15a	190	220	....	Ventricular tachycardia
273′10″	....	...	...	....	Quinidine 10 mg.
273′20″	15b	160-A	125-A	....	Ventricular tachycardia, followed by standstill of ventricle for 24 seconds and of auricle for 10 seconds; convulsion
274′30″	15d	...	180	....	Ventricular tachycardia
299′	16a	...	200	....	Ventricular tachycardia
299′10″	....	...	...	....	Quinidine 10 mg.
299′30″	16b	...	210	....	Ventricular tachycardia; multiple foci
312′	17	...	200	....	Ventricular tachycardia; multiple foci; found dead following morning
Experiment P-1 † (5/27/31)					Digitalis at 15, 47 and 18 minutes
86′	8a	...	200	....	Ventricular tachycardia
86′30″	....	...	...	....	Quinidine 2 mg.
89′	9a	...	230	....	Ventricular tachycardia
89′30″	....	...	...	....	Quinidine 4 mg.
90′	9b	160	200	....	Ventricular tachycardia
92′30″	....	...	...	....	Quinidine 4 mg.
94′	11	200	200	0.10	Sinus rhythm
101′30″	13	150	150	0.10	Ventricular ectopic beats appear
110′	14a	200	220	....	Ventricular tachycardia
110′15″	....	...	...	....	Atropine sulphate 1 mg.
111′	14c	250	250	0.10	Sinus rhythm
117′	15	230	230	....	Ventricular tachycardia
Experiment P-2 (5/28/31)					Digitalis at 10 minutes; marked A-V block
18′	6a	...	240	....	Ventricular tachycardia
79′	....	...	...	....	Quinidine 2 mg.
80′	6b	...	250	....	Ventricular tachycardia
83′15″	....	...	...	....	Quinidine 2 mg.
84′	7b	...	250	....	Ventricular tachycardia
92′45″	....	...	...	....	Quinidine 4 mg.
114′30″	8a	...	210	....	Ventricular tachycardia
115′45″	....	...	...	....	Quinidine 4 mg.
116′	8b	250	A	....	Asystole for 5 seconds
118′	8d	250	140	....	A-V dissociation with nodal beats
151′	9	250	140	....	A-V dissociation with frequent ventricular and nodal beats
Experiment T-2					Digitalis at 3, 25 and 40 minutes
52′	5a	...	240	....	Ventricular tachycardia
52′10″	....	...	...	....	Quinidine 5 mg.
63′	6a	...	240	....	Ventricular tachycardia; Q-R-S of varying forms
63′15″	....	...	...	....	Quinidine 10 mg.
65′	6b	160	130	....	Idioventricular rhythm; Q-R-S of varying forms; this rhythm lasted 2½ minutes
71′	7a	...	220	....	Ventricular tachycardia
71′10″	....	...	...	....	Quinidine 5 mg.
72′	7b	190	115	....	Idioventricular rhythm
80′55″	....	...	...	....	Quinidine 5 mg.
81′	9b	210	75	....	Idioventricular rhythm
82′	9c	...	150	....	Ventricular tachycardia
97′	11	210	80	....	Idioventricular rhythm
101′	12	210	60	....	Idioventricular rhythm
113′	13	250	195	....	Ventricular tachycardia established during retching

* Asystole.

† The experiments are designated so as to indicate when an animal was used on more than one day. For example, experiments P-1 and P-2 indicate that animal P was used for two separate experiments.

TABLE 1.—*Abridged Protocols of the Experiments—Continued*

Time	Tracing	Rate: Auricle	Rate: Ventricle	P-R Interval	Comment
Experiment T-2—Continued					
147′	15	210	75	....	Idioventricular rhythm
					Digitalis at 220 and 244 minutes
257′	24a	...	200	....	Ventricular tachycardia
257′ 5″	....	...	...	....	Quinidine 5 mg.
257′15″	24b	A	70	....	Idioventricular rhythm
	24c	...	150	....	Ventricular tachycardia
	24d	200	A	....	Asytole lasted 5 seconds
	24e	214	90	....	Idioventricular rhythm
301′15″	24f	...	170	....	Ventricular tachycardia
347′	29	...	170	....	Ventricular tachycardia; found dead following morning
Experiment J-1 (5/19/31)					
0′	1	100	100	0.115	Control
30′	....	...	...	.....	Quinidine 2 mg.
31′	2	130	130	0.100	Digitalis at 40 and 301 minutes
316′	9a	134	160	.....	Ventricular tachycardia
320′	....	...	...	.....	Quinidine 2 mg.
320′5″	9b	93	100	.....	Sinus rhythm with frequent ventricular presystolic contraction and dropped beats
320′15″	9c	166	166	.....	A-V dissociation; ventricle responds to A-V node
320′35″	9d	210	210	0.100	Sinus rhythm
321′	9e	...	...	.....	Rhythm alternating between that of 9c and 9d
322′	10	90	82	0.12-0.20	Sinus rhythm; occasional dropped beat
323′	11	120	130	0.12-0.20	Sinus rhythm with ventricular premature contraction
357′	12a	166	200	....	Ventricular tachycardia
359′	....	...	...	....	Quinidine 2 mg.
360′	12b	220	220	0.12	Sinus rhythm
360′30″	12c	180	180	0.12	Sinus rhythm with frequent ventricular premature contraction
Experiment J-2 (5/20/31)					
0′	15a	165	180	....	Ventricular tachycardia
0′10″	....	...	...	....	Quinidine 2 mg.
0′30″	15b	220	220	0.16	Sinus rhythm
1′	15c	...	185	....	Ventricular tachycardia
10′	16a	...	190	....	Ventricular tachycardia
10′30″	....	...	...	....	Quinidine 2 mg.
11′	16b	220	220	0.16	Sinus rhythm
13′	16c	...	220	....	Ventricular tachycardia
Experiment J-3 (5/26/31)					
0′	1	128	128	0.110	Control; sinus rhythm
					Digitalis at 2, 14 and 22 minutes; sinus slowing to 100 and partial A-V block before ventricular tachycardia
48′	8a	...	250	....	Ventricular tachycardia
48′10″	....	...	...	....	Quinidine 2 mg.
49′	8b	...	250	....	Ventricular tachycardia
50′	8c	...	270	....	Ventricular tachycardia
70′	....	...	...	....	Convulsion; death
Experiment V-2					
0′	1	110	110	0.090	Control; digitalis at intervals from 1 to 237 minutes
237′	9	214	130	0.160	Dropped beats
238′	10	...	210	.....	Ventricular tachycardia
241′	11	214	A	.....	Standstill immediately after needle was inserted into vein; lasted 30 seconds; convulsion
247′	11c	...	190	.....	Ventricular tachycardia
247′10″	11d	200-A	A	.....	Standstill lasting about 75 seconds, due to insertion of needle; convulsions
250′	13a	214	200	.....	Ventricular tachycardia
250′ 5″	....	...	...	.....	Quinidine 5 mg.
250′10″	13c	188	A	.....	Ventricular standstill lasting 30 seconds, the last portion showing ventricular fibrillation; convulsion
250′15″	13d	...	210	.....	Ventricular tachycardia
251′	13e	A	A	.....	Asystole of auricle and ventricle for 15 seconds
264′	14a	...	180	.....	Ventricular tachycardia
264′ 5″	....	...	...	.....	Quinidine 5 mg.
264′10″	14c	214-A	A	.....	Standstill for 65 seconds; auricle stopping 10 seconds after ventricle; respiration ceased temporarily; convulsion

TABLE 1.—*Abridged Protocols of the Experiments—Continued*

Time	Tracing	Rate		P-R Interval	Comment
		Auricle	Ventricle		
Experiment V-2—Continued					
284′	16a	...	180	.....	Ventricular tachycardia
284′10″	....	...	...	.....	Physiologic sodium chloride, 5.7 cc.
286′	16b	...	180	.....	Ventricular tachycardia
303′	17a	...	160	.....	Ventricular tachycardia
303′ 5″	....	...	...	.....	Quinidine 2 mg.
303′20″	17b	...	140	.....	Ventricular tachycardia
303′25″	17d	188-A	A	.....	Convulsion; respiration ceased; death
Experiment W-2					
0′	1	130	130	0.10	Digitalis at 29 and 57 minutes
78′	5a	188	210	....	Ventricular tachycardia
78′ 5″	....	...	...	....	Quinidine 2 mg.
78′25″	5d	200	200	0.10-0.16	Sinus rhythm
79′30″	5f	170	170	0.10-0.16	Sinus rhythm
92′	7a	200	210	....	Ventricular tachycardia reappeared at 80 minutes
92′ 5″	....	...	...	....	Quinidine 5 mg.
92′10″	7b	188	130	....	Ventricular tachycardia
94′30″	8	240	120	0.24	Sinus rhythm with 2:1 block; ectopic beats reappeared in 3 minutes
198′	12a	214	190	....	Ventricular tachycardia
198′ 5″	....	...	...	....	Quinidine 5 mg.
198′10″	12b	200	170	....	Ventricular tachycardia
199′	12c	214	200	....	Ventricular tachycardia
214′30″	....	...	...	....	Quinidine 5 mg.
222′30″	15a	...	200	....	Ventricular tachycardia
222′40″	....	...	...	....	Quinidine 10 mg.
223′	15b	...	200	....	Ventricular tachycardia; change in form of Q-R-S
235′	18a	...	170	....	Ventricular tachycardia; multiple Q-R-S forms
235′10″	....	...	...	....	Quinidine 10 mg.
235′15″	18b	160	100	....	Ventricular tachycardia
235′20″	18c	A	A	....	Standstill lasting 15 seconds; convulsion during this peroid
238′	18d	A	80	....	Idioventricular rhythm
245′	....	...	...	....	Quinidine 10 mg.; clonic convulsions
252′	19	...	160	....	Ventricular tachycardia
Experiment Q-1 (6/3/31)					Double vagotomy 2 hours previously; digitalis at 0, 51 and 96 minutes
98′	10	210	120	0.18	Sinus rhythm with dropped beats and ventricular premature contraction
119′	12a	210	200	....	Ventricle tachycardia
119′ 5″	....	...	...	....	Quinidine 2 mg.
119′25″	12b	210	80	....	A-V dissociation; ventricle now responds to A-V node
163′45″	16a	210	120	....	A-V dissociation as in 12b; reappearance of some Q-R-S groups of 12a
163′55″	....	...	...	....	Quinidine 2 mg.
165′25″	16b	210	120	....	A-V dissociation as in 12b; disappearance of Q-R-S groups of 12a
165′35″	16c	170	170	0.18	Sinus rhythm lasting 40 seconds
211′45″	19	210	60	....	A-V dissociation; Q-R-S groups of type in 12b
Experiment S					Double vagotomy 2 hours previously; digitalis at 30 minutes and at 79 minutes, 30 seconds
109′30″	4a	214	230	....	Ventricular tachycardia
109′40″	....	...	...	....	Quinidine 2 mg.
110′10″	4b	...	180	....	Ventricular tachycardia
147′	5a	230	220	....	Ventricular tachycardia
147′ 5″	....	...	...	....	Quinidine 1 mg.
147′25″	5b	230	220	....	Ventricular tachycardia
156′	6a	...	230	....	Ventricular tachycardia
156′ 8″	....	...	...	....	Quinidine 3 mg.
156′18″	6b	...	190	....	Ventricular tachycardia
156′33″	6c	...	140	....	Ventricular tachycardia
156′37″	6d	214-A	A	....	Standstill of ventricle for 15 seconds and of auricle for 7 seconds; convulsion
156′52″	6e	...	170	....	Ventricular tachycardia
157′	6f	...	160	....	Ventricular tachycardia
Experiment R-1 (6/17/31)					Double vagotomy 2 hours previously; digitalis at 33 and 60 minutes
79′	9a	190	220	0.12	Ventricular tachycardia interrupted by an occasional normal beat
79′10″	....	...	...	....	Quinidine 2 mg.
75′45″	9b	180	180	0.12	Fewer ectopic beats

TABLE 1.—*Abridged Protocols of the Experiments—Continued*

Time	Tracing	Rate		P-R Interval	Comment
		Auricle	Ventricle		
Experiment R-1—Continued					
88′	10	190	190	0.12	Sinus rhythm
100′	11	200	200	0.14	Sinus rhythm
110′	12	200	200	0.16	Numerous ectopic beats reappear
125′	13	200	140	0.17	Sinus rhythm with dropped beats
160′	15	200	140	0.17	Same as 13
Experiment R-2 (6/18/31)					Digitalis at 20 minutes
49′	18	170	215	....	Ventricular tachycardia
64′	20a	190	215	....	Ventricular tachycardia
64′11″	....	...	...	....	Quinidine 4 mg.
64′41″	20b	190	200	....	Ventricular tachycardia
69′	21a	190	210	....	Ventricular tachycardia
69′11″	....	...	...	....	Quinidine 8 mg.
69′36″	21b	...	175	....	Ventricular tachycardia
72′	22a	...	200	....	Ventricular tachycardia
72′20″	....	...	...	....	Quinidine 16 mg.
72′30″	22b	A	160-A	....	Ventricular tachycardia; cardiac standstill for 25 seconds; only 82 ventricular beats of various foci in following 3 minutes; several convulsions
78′30″	23	120	120	....	A-V dissociation; ventricle irregular and Q-R-S groups of varying forms; tonic convulsion
81′	....	...	...	....	Tonic convulsion
83′	24	...	180	....	Ventricular tachycardia
238′	26a	160	190	....	Ventricular tachycardia
238′16″	....	...	...	....	Quinidine 12 mg.
238′26″	26b	...	150	....	Ventricular tachycardia; in next 4 minutes, A-V dissociation with periods of auricular asystole, auricular rates at 90 and ventricular rates from 30 to 140, brief periods of these phenomena alternating
247′	27	...	155	....	Ventricular tachycardia
251′	28	...	150	....	Ventricular tachycardia
263′	29	A	90	....	A-V dissociation; beats of different foci

electrocardiographic changes which have been observed, some of them having occurred under conditions that make a satisfactory interpretation impossible. The following are the essential changes produced by the injection of quinidine in the course of these experiments:

1. Tonic convulsions due to ventricular standstill (chart 1*A*, tracing 24*d*).

2. Slowing of the ventricular tachycardia (chart 1*B*, tracings 10*a* and 10*b*).

3. Disappearance of the ventricular tachycardia followed by a normal sinus rhythm that was slower than the ectopic rhythm (chart 1*C*, tracings 5*b* and 5*f*; chart 2*A*, tracings 10 and 13).

4. Disappearance of the ventricular tachycardia followed by a normal sinus rhythm that was faster than the ectopic rhythm (chart 2*A*, tracings 10 and 11).

5. Disappearance of the ventricular tachycardia followed by A-V dissociation in which the ventricle responded to the A-V node (chart 2*B*, tracings 12*a* and 12*b*).

6. Disappearance of the ventricular tachycardia, followed by a slow idioventricular rhythm which was usually very irregular (chart 1*A*, tracings 24*b* and 24*e*; chart 2*C*, tracings 22 and 23).

7. Changes in the forms and duration of the Q-R-S groups (chart 2*C*, tracings 21*b* and 22).

8. Acceleration, slowing or asystole of the auricle (chart 1*A*, tracing 24*b*; chart 2*A*, tracings 11 and 13).

Convulsions.—Large doses of digitalis rapidly injected intravenously in the dog may produce a temporary ventricular standstill or marked

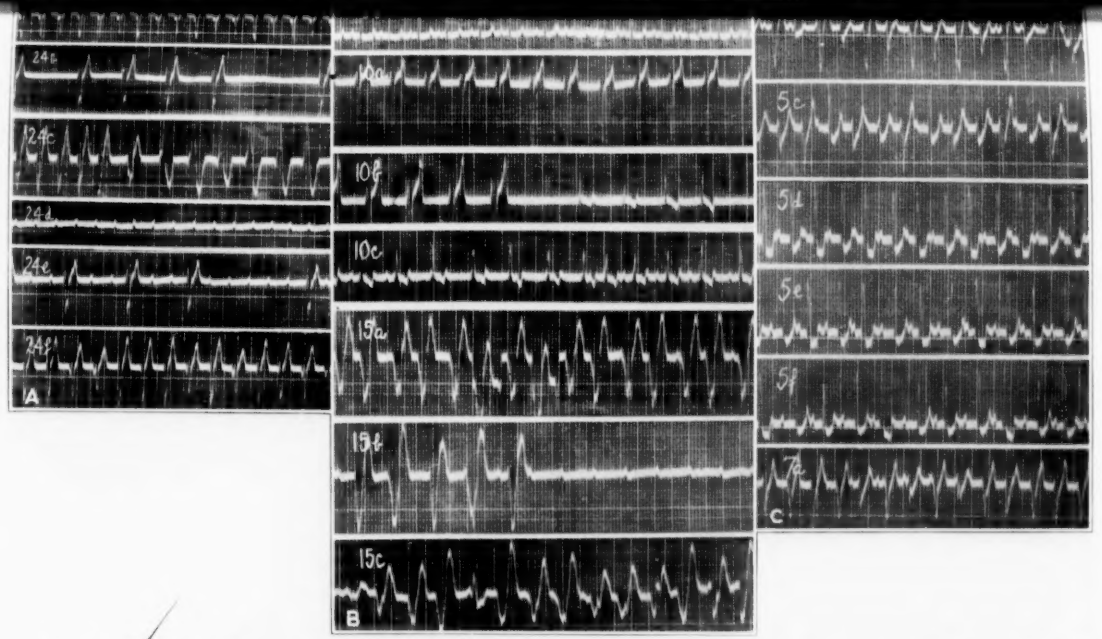

Chart 1.—*A*, selected tracings from experiment T-2: 257 minutes, (*24a*), ventricular tachycardia, rate 200; 257 minutes and 35 seconds (*24b*), immediately after 5 mg. of quinidine, ventricular rate 80; 257 minutes and 40 seconds, (*24c*), ventricular rate 150; 257 minutes and 50 seconds (*24d*), ventricular asystole, auricular rate 200; 258 minutes (*24e*), ventricular rate 90, auricular rate 214; 259 minutes and 30 seconds (*24f*), ventricular rate 170. *B*, selected tracings from experiment N: 214 minutes and 30 seconds (*8b*), sinus rhythm, rate 160; 236 minutes and 15 seconds (*10a*), 4 minutes after digitalis, ventricular rate 160; 236 minutes and 40 seconds (*10b*), 10 seconds after 5 mg. of quinidine, ventricular rate 125; 237 minutes and 30 seconds (*10c*), rate 150; 273 minutes, (*15a*), ventricular rate 220; 273 minutes and 20 seconds (*15b*), 10 seconds after 10 mg. of quinidine; 274 minutes (*15c*), ventricular rate 150. *C*, selected tracings from experiment W-2: 78 minutes (*5b*), ventricular rate 210, auricular rate 188; 78 minutes and 20 seconds (*5c*), 20 seconds after 2 mg. of quinidine, ventricular rate 210; 78 minutes and 25 seconds (*5d*), rate 200; 78 minutes and 45 seconds (*5e*), rate 190; 79 minutes and 30 seconds (*5f*), rate 170; 92 minutes (*7a*), ventricular rate 210, auricular rate 200.

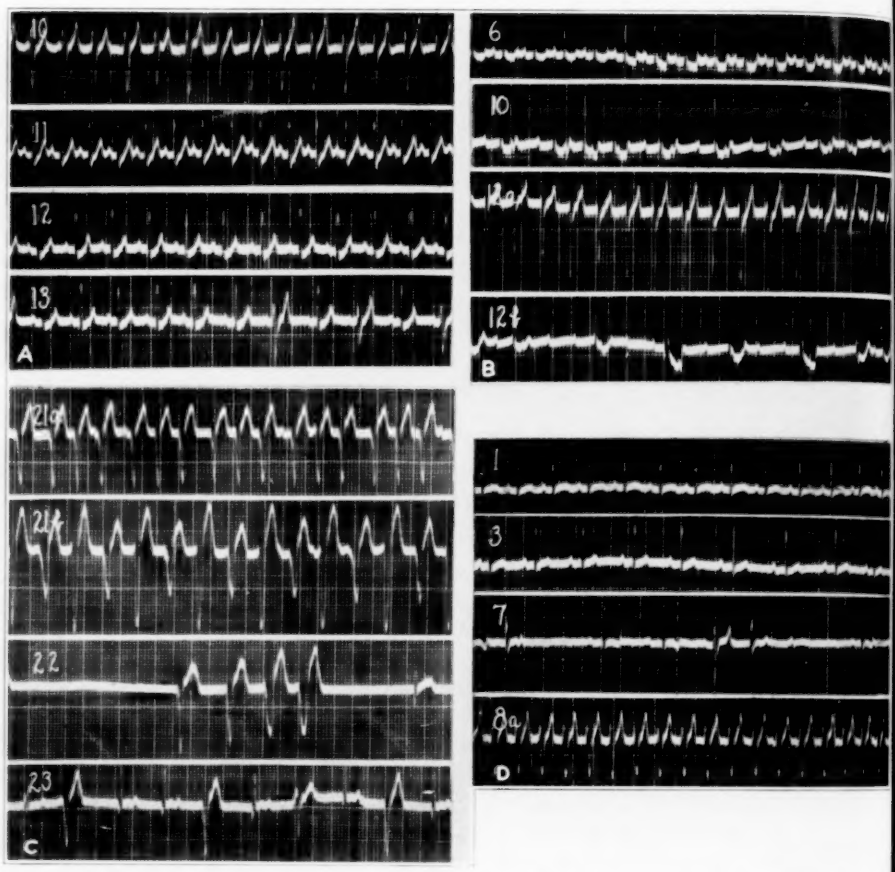

Chart 2.—*A*, selected tracings from experiment P-1: 91 minutes (*10*), ventricular rate 190, auricular rate 188; 94 minutes (*11*), 25 seconds after 4 mg. of quinidine, heart rate 200; 98 minutes (*12*), heart rate 180; 101 minutes and 30 seconds (*13*), heart rate 150, premature beats. *B*, selected tracings from experiment Q-1: 75 minutes (*6*), after digitalis; 112 minutes (*10*), after additional digitalis; 133 minutes (*12a*), ventricular rate 200, auricular rate 210; 133 minutes and 30 seconds (*12b*), 25 seconds after 2 mg. of quinidine, ventricular rate 120, auricular rate 214. *C*, selected tracings from experiment R-2: 69 minutes (*21a*), ventricular rate 210, auricular rate 190; 69 minutes and 36 seconds (*21b*), ventricular rate 175, after second dose of quinidine; 72 minutes and 30 seconds (*22*), after third dose of quinidine; 78 minutes and 30 seconds (*23*), only 82 ventricular beats in three minutes. *D*, selected tracings from experiment P-1: 0 minutes (*1*), normal sinus rhythm, rate 130; 38 minutes (*3*), 23 minutes after 0.5 cat unit of digitalis, rate 110; 79 minutes and 30 seconds (*7*), after additional 0.4 cat unit of digitalis; 86 minutes (*8a*), ventricular tachycardia, ventricular rate 260.

ventricular slowing with irregularities in rhythm, these being attended frequently by a severe systemic disturbance (wild agitation, crying, respiratory distress). Such symptoms usually pass off in from five to ten minutes, and the cardiac slowing is followed by ventricular tachycardia (chart 2 *D*). In the normal dog digitalis in fatal doses causes asphyxial convulsions of a tetanic type owing to circulatory failure ensuing from the ventricular fibrillation. Under certain conditions a reflex may cause sudden standstill of the heart in which digitalis has produced a ventricular tachycardia, although the latter rhythm alone usually results from only 60 or 70 per cent of the fatal dose. Such a reflex standstill may last long enough to cause death in the partially poisoned heart. A reaction much like this was observed in one of the animals in the present series of experiments (experiment V-2). This animal received a total of 1.5 cat units of digitalis per kilogram in a period of about four hours. Eight minutes after a ventricular tachycardia was induced, the insertion of the hypodermic needle of the syringe containing the quinidine was followed promptly by ventricular asystole lasting thirty seconds, the auricle during this period continuing at a rate of 214 per minute. Quinidine had not been injected. This procedure was repeated six minutes later and was followed by a similar result, sudden ventricular standstill lasting seventy-five seconds, the auricle ceasing to beat about ten seconds after the ventricle and resuming its beat about twenty-five seconds before the ventricle. Subsequently this effect could not be elicited by the reflex or by the injection of salt solution, but was repeatedly produced by small doses of quinidine. In another experiment, which is not included in the tables, and in which ventricular tachycardia was induced by digitalis, the application of a sponge containing amyl nitrite to the nose caused prompt disappearance of the ectopic rhythm followed by a period of complete asystole. That this was also probably due to a reflex rather than to the direct action of the amyl nitrite on the heart was in evidence from the fact that much more intense action after several minutes of inhalation of amyl nitrite did not again abolish the ventricular tachycardia. As already stated, however, ventricular standstill is not the usual mode of death in the dog and in almost all cases in which digitalis in a fatal dose is injected intravenously in a short period of time and a ventricular tachycardia is produced, death results from ventricular fibrillation and is attended by an asphyxial convulsion. Similar results with digitalis were obtained by Rothberger and Winterberg,[6] who reported that with rapid poisoning death occurred as the result of ventricular fibrillation, while with slower poisoning cardiac standstill was produced.

6. Rothberger, C. J., and Winterberg, H.: Ueber den Einfluss von Strophanthin auf die Reizbildungsfähigkeit der automatischen Zentren des Herzens, Arch. f. d. ges. Physiol. **150**:217, 1913.

It was shown in the previous study [3] that quinidine induces clonic convulsions in the normal dog. This resulted in every instance after total doses of from 21 to 40 mg. It was in no case associated with any disturbance in cardiac rhythm. The convulsant action of quinidine is probably directly on the central nervous system.

In the digitalized dog quinidine produces two types of convulsions. Those occurring with smaller doses are not clonic but tonic. They are not due to direct action on the central nervous system but to cardiac standstill. They occurred in five of seven dogs (V-2, W-2, R-2, S and N), when the ventricular asystole lasted from about fifteen to sixty-five seconds. In two instances (P-2 and T-2) in which the asystole was of shorter duration, about five seconds, there was no change in the respiration or any other external manifestation indicating a cardiac disturbance. Whereas the smallest dose that induced convulsions in the normal animal was 21 mg., doses as small as 5 or 6 mg. of quinidine sufficed to cause a tonic convulsion during digitalis poisoning. The contrast between the results following quinidine alone [3] and those after quinidine during digitalis poisoning were striking in the animals of experiments V-2 and W-2. In the animal of experiment V-2, 30 mg. of quinidine given in a period of thirty-four minutes induced clonic convulsions; four days later (after all the quinidine had been excreted), in the presence of ventricular tachycardia induced by digitalis, as small a dose as 5 mg. of quinidine caused tonic convulsions due to cardiac standstill. Similarly in the animal of experiment W-2, 40 mg. of quinidine alone given in a period of thirty-two minutes induced clonic convulsions; six days later, in the presence of ventricular tachycardia produced by digitalis, 30 mg. of quinidine given in thirty-seven minutes caused tonic convulsions due to cardiac standstill.

Clonic convulsions of the type occurring in normal animals after quinidine were seen in only one experiment in the digitalized dogs (experiment W-2). In this case a tonic convulsion due to cardiac standstill occurred after 30 mg.[7] had been injected in thirty-seven minutes, and a series of clonic convulsions after an additional 10 mg. given ten minutes later. The latter convulsions were not attended by ventricular asystole, and it is possible that the impulses discharged during the violent convulsions excited the ventricle to prevent standstill, which might have occurred after this additional dose. The failure to produce the clonic convulsions more often in this series was probably due to inadequate dosage effective at the same time, the interval between the last two fractions being too long, even in those cases in which the total quantity injected corresponded to the convulsant doses

7. The additional doses of quinidine seen in table 1, experiment W-2, are not included because of the long interval intervening.

given to normal animals. It is probable that the digitalis poisoning does not appreciably change the response of the animal to the convulsant action of quinidine on the central nervous system. In the one (experiment W-2) in which clonic convulsions occurred, the total dose of 40 mg.[8] in about forty-five minutes was similar to that necessary in normal animals.

Effect on Rate and Rhythm of the Ventricle.—Some of the studies on the combined actions of digitalis and quinidine were carried out without electrocardiographic tracings. Estimations of the beneficial or injurious effects were made from myocardiographic and carotid blood pressure curves, the essential records being a change in the rate or regularity of the deflections. A change in the rate or regularity of rhythm is, however, no guide as to the nature of the change in the cardiac mechanism produced by quinidine. For example, it was frequently found that a regular rhythm during digitalis poisoning was replaced by an irregular rhythm after quinidine. This might have appeared as an undesirable change in a carotid pressure curve; yet in the electrocardiogram this was often found to be due to change from a regular ventricular tachycardia, which is an advanced toxic rhythm, to regular sinus rhythm with ventricular premature contractions (chart 2*A*, tracings 10 and 13). A few examples may be mentioned of the numerous combinations of changes in the rate and rhythm in relation to changes in the cardiac mechanism that occurred during the course of the experiments: In experiment W-2 an irregular rhythm became regular and slower, while at another time the reverse occurred, a regular rhythm becoming irregular and slower; yet in both cases the mechanism remained a ventricular tachycardia. In other instances a rhythm remained regular as before, although an important change in the mechanism had taken place, a ventricular tachycardia having been abolished and replaced by a normal sinus rhythm, the latter being attended either by a negligible change in the rate (experiment P-1, chart 2*A*), or by marked slowing (experiment W-2) or marked acceleration of the cardiac rate (experiment J-1).

Slowing of the Ventricular Tachycardia.—One of the most constant effects following the administration of quinidine after digitalis had produced a ventricular tachycardia was a reduction in the rate of the ectopic rhythm. This occurred after each of twenty-seven injections of quinidine in ten animals, and after initial doses of as little as from 1 to 5 mg. An average rate of the ventricular tachycardia of 206 per minute was reduced to one of 154 per minute, an average slowing, therefore, of 52 beats per minute, based on the results obtained in different

8. Only 40 mg. is regarded as the effective dose in this case because more than two hours had elapsed since the previous doses were given.

animals after varying doses of digitalis and quinidine. The amount of slowing in different cases varied widely, between 10 and 130 beats per minute. The striking differences between the changes in the ventricular rate produced by quinidine before and after digitalis in the same animals are shown in table 2, in which comparable sections of the two sets of experiments are brought together.

In several instances the ventricular tachycardia slowed progressively with marked changes in the forms of the Q-R-S groups resulting in idioventricular rhythms with rates of 70 or 80 a minute, or slower, and usually attended by marked irregularity in the rhythm of the ventricle (chart 1*A*, tracings 24*b* and 24*c*; chart 2*C*, tracings 22 and 23). In most cases, however, the slowing was followed by an abrupt cessation of the ventricular tachycardia with the establishment of one of several

TABLE 2.—*Comparison of the Effects of Similar Doses of Quinidine on the Ventricular Rate Before Digitalis and After Digitalis Had Induced Ventricular Tachycardia in the Same Animals* *

	Before Digitalis			After Digitalis		
Experiment	Dose of Quinidine, Mg.	Change in Rate		Dose of Quinidine, Mg.	Change in Rate of Ventricular Tachycardia	
		From	To		From	To
J-1	2	100	130	2	160	100‡-210
T-1, 2	17†	140	230	15†	240	130
W-1, 2	30†	120	170	30†	160	100-standstill
V-1, 2	10	125	180	10	200	180-standstill

* The rate of the ventricle before the digitalis is in response to the auricle (normal sinus rhythm), while after digitalis there is a ventricular tachycardia (A-V dissociation).

† These doses were given in fractions. The intervals between the fractions are given in table 1 of this paper in the case of the digitalized dogs, and in the previous study [3] in the case of the normal dogs.

‡ The rate of 100 in this case was a sinus rhythm with frequent ventricular premature beats, which was followed by a sinus tachycardia.

new temporary mechanisms: ventricular asystole, normal sinus rhythm or nodal rhythm. In only one instance was quinidine followed by ventricular fibrillation; this occurred in experiment V-2 after ventricular standstill for about fifteen seconds. This is the animal which had received a very large dose of digitalis (1.5 cat units per kilogram) and in which the insertion of the needle into the vein was followed by periods of auricular and ventricular asystole.

Ventricular Asystole.—In seven of ten animals the disappearance of the ventricular tachycardia was followed by a standstill of the ventricle for periods varying from five to sixty-five seconds in duration and attended in most cases by asphyxial convulsions. The ventricular standstill was often followed by a short period of ventricular tachycardia, which terminated spontaneously in another period of asystole. For example, in experiment V-2 (table 1, tracings 13*a*, 13*c*, 13*d* and 13*e*) a dose of 5 mg. of quinidine induced a period of asystole lasting thirty

seconds, which was followed by a period of ventricular tachycardia lasting twenty-five seconds, the latter in turn being followed by a second period of asystole lasting fifteen seconds. In some experiments evidence of marked fatigability of intraventricular conduction followed the disappearance of the ventricular tachycardia, as seen from the progressive prolongation of the Q-R-S time from beat to beat (chart 2*C*, tracing 22). The significance of these observations will be considered later.

In the cases in which the ventricular tachycardia was followed by asystole the final rate of the ventricle before the standstill varied from 100 to 185 in different experiments, but there appeared to be a fairly fixed final rate before its abrupt cessation in the same animal at different times and with different doses of quinidine. This fact is strikingly illustrated in experiments N and V-2. In experiment N after 5 mg. of quinidine, the ventricular tachycardia of 160 slowed to 125 per minute, after which it terminated abruptly; about an hour later, after 10 mg. of quinidine, a ventricular tachycardia of 220 also terminated abruptly, the final rate again being 125 a minute (chart 1*B*). In experiment V-2, the ventricular asystole appeared in each of four instances when the rate of the tachycardia was diminished to about 185 per minute. This effect was due to 5 and 10 mg. doses of quinidine respectively, in two instances, and to a reflex action in two others. The fifth period of asystole, during which the animal died, was preceded by a ventricular tachycardia with a rate as low as 140 a minute. This reduction in rate occurred about forty-five minutes after the previous effects and was probably due to the changes induced in the heart by the previous repeated and prolonged periods of cardiac standstill.

Restoration of a Sinus Rhythm.—A normal sinus rhythm was produced by each of nine injections of quinidine in six animals. In eight instances a ventricular tachycardia was thereby abolished; in one, a nodal tachycardia (experiment Q-1). The rate of the new rhythm was extremely variable, in some cases slower and in some faster than the one it replaced, both rhythms being occasionally seen in the same animal after one dose. At least two factors, therefore, may play a rôle in the establishment of a normal sinus rhythm by quinidine, namely, sinus acceleration (probably owing to depression of the vagus) and direct slowing of the ventricular ectopic rhythm, these two frequently taking part at the same time. There are cases, however, in which the main action is sinus acceleration, and in these the abolition of the idioventricular tachycardia may be more apparent than real, the faster sinus becoming the pacemaker and simply masking the rapid rhythm of the ventricle poisoned by digitalis (after 2 mg. of quinidine in experiment J-2). The action of quinidine in such a case may be essentially similar

to that of atropine (experiment P-1). In other cases sinus acceleration does not play an important part in the establishment of a normal rhythm because the latter is slower than the rhythm which it has replaced. The part played by the direct action of quinidine on the ventricle in the reestablishment of the normal rhythm is more clearly in evidence in the vagotomized animals in which sinus acceleration is sometimes not so prominent a factor (experiment R-1).

The dose of quinidine that sufficed to induce a normal sinus rhythm was very small, 2 mg. being effective in six of nine injections, and the largest effective dose being 5 mg. When such doses failed to induce a sinus rhythm, larger doses were also ineffective. This is due to the fact that in the latter cases digitalis had induced an A-V block [9] in addition to the ventricular tachycardia, so that a normal sinus rhythm was no longer possible even though acceleration of the auricle had occurred, and now the only action of quinidine that could influence the rate and rhythm of the ventricle was the action directly on the ventricle. This is found in several experiments, but is especially well illustrated by repeated doses in experiment W-2. Thus a dose of 2 mg. established a normal sinus rhythm with a P-R interval that had increased from a normal of 0.10 second before the digitalis to 0.16 second; during the following fourteen minutes, after the intensity of digitalis action had increased, a dose of 5 mg. again abolished a ventricular tachycardia and reestablished a sinus rhythm, but there was now a higher degree of A-V block (P-R 0.28, and 2:1 rhythm); after an interval of one hundred and six minutes, the tracing showed definite evidence of complete A-V block (auricular rate 215, ventricular tachycardia 190), and at this time a dose of 5 mg. simply slowed the ventricular tachycardia, but in the presence of the complete block failed to reestablish a sinus rhythm.

Effect on the Auricle.—In most instances the rapid ventricular rate masked the P waves, so that the rate of the auricle could not be ascertained. An examination of table 1, however, shows that in several cases in which the changes in the rate of the auricle could be followed, quinidine in the overdigitalized heart produced either acceleration or slowing or standstill of the auricle. There was no strict parallelism between the changes in the ventricular and auricular rates. In the cases in which small doses of quinidine were used, there was an indication that the ventricular tachycardia was more sensitive than the auricular tachycardia to the direct depressant action of the drug, although this may be more

9. The larger doses of quinidine might conceivably have contributed to the depression of conduction in the digitalized dog as it did in the experiments of Lewis and others under other conditions, although in the normal dog, depression of A-V conduction was never seen after quinidine in our experiments.

apparent than real in some cases, because direct depressant action on the sinus may be masked by simultaneous depression of the vagus. Nevertheless, in some instances a considerable effect on the ventricle was in evidence when no effect on the auricular rate could be detected, while the reverse was not seen; in experiment N (tracing 14*b*), a 5 mg. dose of quinidine slowed the ventricular tachycardia from 190 to 160, while the rate of the auricle remained at 190 a minute; in experiment P-2 (tracings 8*b* and 8*d*), the last dose of 4 mg. of quinidine produced complete standstill of the ventricle with no appreciable change in the auricular rate of 250 per minute. This was also seen in experiment Q-1 (tracing 12*b*), in which the vagi were excluded by vagotomy; a 2 mg. dose of quinidine abolished the ventricular tachycardia, while no influ-

TABLE 3.—*Comparison of Normal and Digitalized Dogs with Reference to Changes in the Auricular Rate Following the Administration of Quinidine*

	Normal Dog			Digitalized Dog		
	Dose of Quinidine,	Change in Rate		Dose of Quinidine,	Change in Rate	
Experiment	Mg.	From	To	Mg.	From	To
Q-1 (vagotomized)	..	...	...	2	210	170
R-2 (vagotomized)	..	...	...	28*	190	Standstill
S (vagotomized)	..	...	...	3	214	Standstill
Y-1 (vagotomized)	2	210	230			
X-1 (vagotomized)	27*	150	195			
Z (vagotomized)	5	160	120			
N-2	..	...	...	5 20	5 190	Standstill Standstill
J-1	2	100	130	2	134	90
T-1, 2	5	138	190	5	210	Standstill
V-1, 2	10	125	180	10*	214	Standstill
W-1, 2	40*	160	210	37*	214	Standstill

* These were injected in fractional doses. The exact intervals between doses are given in table 1. The table does not give all the results obtained in normal animals,[3] but only selected experiments with comparable doses of quinidine, which emphasizes the difference between the type of reactions seen in normal and in digitalized animals.

ence on the auricular rate of 210 was in evidence. At other times the changes in the auricle and ventricle ran parallel. The larger doses which caused ventricular asystole usually caused auricular asystole as well; thus, in experiment N (tracing 15*b*) a dose of 10 mg. of quinidine caused slowing of the auricle and ventricle which terminated in complete standstill of both. Frequently, the change in the rate of the auricle ran in a direction opposite to that of the ventricle, the auricle being accelerated, owing to depression of the vagi, and the ventricular tachycardia slowed, owing to direct action on the ventricle (experiment P-1, tracings 9*b*, 11 and 13). This was frequently the mode by which a normal sinus rhythm was reestablished.

An interesting aspect of the auricular response to quinidine in the digitalized animal is the slowing and complete standstill of the auricle. The standstill of the auricle, like that of the ventricle, is also usually abrupt after an initial period of slowing. Sometimes the auricular

deflections cease without any appreciable previous slowing. These changes have been tabulated in table 3 and for emphasis are compared with the usual type of response in normal animals. In the previous study [3] it was shown that sinus acceleration occurred invariably after quinidine in the normal animal, and that in only three of twelve experiments was momentary and moderate slowing observed. Auricular standstill never occurred in the normal animal even after very large doses of quinidine, whereas during the action of digitalis auricular standstill appeared in seven of ten animals, in some after very small doses of quinidine, from 3 to 5 mg. The differences in the response were particularly striking in the four cases (J-1, T-2, V-2 and W-2) in which comparable doses of quinidine were given to the same animals before and after digitalis. The possibility suggested itself that the standstill of the auricle might not be a direct effect of quinidine on the auricle but rather a secondary effect of the ventricular standstill. An examination of the records, however, shows that while in several instances the auricle stopped after the ventricular arrest appeared, there was no fixed order in which the two chambers came to a standstill; in some, asystole appeared in the two at the same time (experiment V-2, tracing 17*d*); in others only the ventricle stopped, or stopped first (experiment N, tracing 15*b*); in still others the auricle was in asystole while the ventricle was beating (experiment W-2, tracing 18*d*).

Effect on A-V and Intraventricular Conduction.—In the previous study [3] it was shown that quinidine depresses intraventricular conduction but does not prolong A-V conduction in the normal unanesthetized dog. Lewis and his co-workers,[10] using fully anesthetized dogs with the thoracic cavity open, found that similar doses of quinidine caused not only prolonged intraventricular, but also markedly impaired A-V conduction. It is clear, therefore, that with a change in the conditions of the experiment, perhaps in this case due to the anesthesia and low blood pressure, quinidine gives different results. We have already shown that digitalis poisoning renders both the auricle (or sinus) and ventricle more susceptible to the depressant action of quinidine so that slowing which is rarely seen in the normal dog becomes the most prominent effect of quinidine during the action of digitalis. Our records have been analyzed for evidence of any effect of quinidine on the P-R intervals in the digitalized dogs. The material was not entirely satisfactory for this purpose for several reasons. In most instances a ventricular tachycardia was induced with digitalis before the quinidine was injected; hence under those conditions A-V conduction time could not be ascer-

10. Lewis, T.; Drury, A. N.; Iliescu, C. C., and Wedd, A. M.: Observations Relating to the Action of Quinidine upon the Dog's Heart: with Special Reference to Its Action on Clinical Fibrillation of the Auricles, Heart **9**:55, 1921.

tained. In many cases digitalis induced varying degrees of heart block which became more intense during the course of the experiment, and when a greater degree of A-V block was present after quinidine than before, there was no way of knowing whether it was due to digitalis, to quinidine or to both, because a greater degree of block that might have been caused by digitalis would be masked by the ventricular tachycardia and would come into view only when the latter was abolished by the quinidine.

In experiment P-1, quinidine diminished A-V block induced by digitalis. Thus, following the digitalis the sinus rate was slowed and the P-R interval prolonged from 0.12 to 0.16 second, with dropped beats (chart *2D*). A dose of 4 mg. of quinidine accelerated the heart rate from 100 to 150 and the P-R interval was shortened to 0.10 second. It is probable that in this instance the chief action of digitalis depended on the vagal tone, and the main action of quinidine was through depression of the vagi.

In one vagotomized dog (experiment Q-2) in which digitalis had induced an A-V block without the ventricular tachycardia, quinidine diminished the block by what appears to be still another mechanism. Digitalis had induced a 2:1 block with a P-R interval of 0.18 second (auricular rate 240, ventricular rate 120). About fifteen seconds after the intravenous injection of 4 mg. of quinidine the block was temporarily diminished, resulting in a 1:1 rhythm with a P-R interval of 0.18 second, the auricular rate having slowed from 240 to 200 per minute during this action. The reduction in the block in this instance was probably due to the slowing of the auricle as the direct effect of the quinidine. This effect of rate on A-V conduction is in harmony with the observations of Lewis and his co-workers.[10]

Our experiments, therefore, afford no indication that quinidine in small doses directly depresses A-V conduction in the digitalized animal. It is, of course, conceivable that it might under suitable conditions cause depression indirectly, namely, through its paretic action on the vagus which by sinus acceleration might give rise to an impairment of A-V conduction.

The normal sinus rhythm established by quinidine, after the ventricular tachycardia was abolished, frequently showed a longer Q-R-S time than before the ectopic rhythm appeared. Thus in experiment W-2, the interval had increased from 0.03 to 0.05 second after 2 mg. of quinidine; in experiment J-1, from 0.03 to 0.04 second after 2 mg. and from 0.04 to 0.06 second after an additional 2 mg.; in experiment P-1, it increased from 0.04 to 0.06 second after several doses totaling 10 mg. Such marked effects following the 2 mg. doses of quinidine were not seen in normal animals, but the difficulties in interpretation are

here much the same as in the case of the P-R intervals, since they may be due to the digitalis action alone on the ventricle, the effect being masked by the ventricular tachycardia, or to the effect of the previous tachycardia itself, as we will show later. These possibilities receive support from the facts that in experiment Q-2, in which ventricular tachycardia did not result from digitalis, two doses of quinidine, 2 and 4 mg. respectively, did not prolong the Q-R-S time beyond the control of 0.03 second, and in experiment N, two doses of quinidine, 2 and 5 mg. respectively, failed to prolong the Q-R-S time of 0.03 second. In this last experiment, after the action of digitalis became sufficiently intense to produce a ventricular tachycardia, an additional dose of 5 mg. of quinidine established a sinus rhythm with a Q-R-S time that had increased from 0.03 to 0.05 second.

We have already stated that quinidine not only slowed the rate of the ventricular ectopic rhythms resulting from digitalis, but frequently produced marked changes in the forms of the Q-R-S groups. As a change in the focus or path of the impulse may alter the Q-R-S time without any direct depression of intraventricular conduction, it was in many cases not possible to ascertain whether such depression had occurred. In several instances, however, the tracing left little doubt that quinidine, even in very small doses, can produce marked depression in intraventricular conduction as measured by the change in the duration of the ectopic Q-R-S groups (chart *2C*, tracings *21a*, *21b* and *22*).

Effect of Vagotomy.—An examination of table 1 shows that after double vagotomy the effects of quinidine on the heart poisoned by digitalis were essentially similar to those in normal digitalized animals. It would be expected that sinus acceleration would not play as important a rôle in the restoration of the normal rhythm in the vagotomized animal, but the experiments are too few to ascertain this fact, and it is probable that even with a larger number of experiments the rôle of the vagi would not be prominent, because, as has been shown in the previous study,[3] the intravenous injection of quinidine may result in considerable acceleration of the sinus rate, even in vagotomized animals.

Effect of Degree of Digitalization on Response to Quinidine.—The results obtained in the same animal made it possible to study the effects of varying doses of quinidine in different stages of digitalis poisoning. They show in several cases (table 1) that the effects of given doses of quinidine depend on the intensity of digitalis action. Thus in experiment J-1, a 2 mg. dose abolished a ventricular tachycardia and reestablished a sinus rhythm after moderate digitalis poisoning, whereas a similar dose of quinidine given several days later

(experiment J-3), after an injection of digitalis that proved to be fatal, produced no effect on the ventricular tachycardia. Similarly, in experiment P-1, a 2 mg. dose of quinidine slowed the rate of the ventricular tachycardia (from 260 to 230), whereas the same dose repeated on the following day, after more intense digitalis poisoning, produced no effect (experiment P-2). In experiment N, a 5 mg. dose of quinidine, injected less than four minutes after digitalis had produced ventricular tachycardia, slowed the latter from a rate of 160 to one of 125 per minute, which was in turn followed by a normal sinus rhythm. When the action of digitalis became more intense within the next twenty-five minutes, as seen by the fact that a ventricular tachycardia with a much higher rate appeared (190 per minute as compared with 160 per minute), the effect of a similar dose of quinidine (5 mg.) was less pronounced; it served simply to slow the ventricular tachycardia to 160, but failed to produce a sinus rhythm. At a still later period (sixty-three minutes after the ventricular tachycardia had been induced by digitalis), a dose of 10 mg. of quinidine failed to produce any change in the rate of the ventricular tachycardia. The failure of the second 5 mg. dose to induce a sinus rhythm was due, as in other cases, to the presence of A-V block, as seen by the fact that the auricular rate was 190 per minute and the ventricle was beating independently at a slower rate of 160. The latter fact is more strikingly brought out by the other observations in this experiment, in that twice the dose of quinidine (10 mg.) injected about ten minutes after the second dose of 5 mg. served merely to produce ventricular asystole for a period of twenty-four seconds, this having been neither preceded nor followed by a sinus rhythm.

Duration of Effects of Quinidine.—It is well known that the toxicity of quinine and quinidine varies greatly with the rate of injection because of the rapid excretion. Gordon, Matton and Levine [11] found that the fatal dose of quinidine sulphate in the cat was about 25 mg. per kilogram when injected intravenously in a single dose. The dose became 45 mg. when injected at the rate of 15 mg. every six minutes and 100 mg. when given in small doses over two hours. Weiss and Hatcher [12] also found that the dose increased with the period of injection, and that in the cat the essential elimination was practically complete within three to four hours. In the previous study [3] it was shown that the effects of quinidine on the electrocardiogram appeared

11. Gordon, B.; Matton, M., and Levine, S. A.: The Mechanism of Death from Quinidine and a Method of Resuscitation: An Experimental Study, J. Clin. Investigation **1**:497, 1925.

12. Weiss, S., and Hatcher, R. A.: Studies on Quinidine, J. Pharmacol. & Exper. Therap. **30**:335, 1927.

within a few seconds after the intravenous injection, almost completely disappeared in most cases in less than from five to ten minutes and were rarely in evidence within a half hour following intravenous administration. The duration of the effects produced by the intravenous injection of quinidine on the abnormal rhythms was much more variable than in the normal animal. On the whole the effect was brief, however, lasting in the majority of instances less than three minutes, in some cases up to about ten minutes, while in a few instances considerable effect was still in evidence after from one-half to one and one-half hours (P-2, T-2, Q-1 and R-1). The duration of the effects of quinidine in the digitalized animals does not depend on the elimination of quinidine alone but on at least two other factors, namely, the partial excretion of digitalis during the few hours of the quinidine experiment, and secondly, on the fact that an ectopic rhythm that has been abolished by quinidine may not necessarily reappear when the quinidine has been excreted. For example, it is well known that the circus movement of auricular fibrillation, after having been abolished by quinidine, may remain in abeyance in some cases for several weeks or months without the use of any additional drug—long after the previous doses have been excreted.

It is probable that the dosage of quinidine bears some relation to the duration of some of the effects, but the conditions of our experiments were so exceedingly variable that no correlation could be detected between these two factors. For example, in experiment Q-1 two doses of 2 mg. each abolished a ventricular tachycardia, and marked slowing of the heart was still in evidence ninety minutes following the first dose, whereas in experiment T-2, two doses of 5 and 10 mg., respectively, abolished the ventricular tachycardia, but in this case the the effect lasted no longer than two and a half minutes.

COMMENT

In the treatment of patients with auricular fibrillation digitalis is usually given to relieve the cardiac failure and quinidine usually to reestablish the normal rhythm. Lewis and his co-workers [13] showed that in those in whom the tendency for digitalis to shorten the refractory time interferes with the action of quinidine, somewhat larger doses of the latter may be necessary to establish the normal rhythm. Viko, Marvin and White [14] were unable to detect any interference with the effectiveness of quinidine in terms of the doses necessary to abolish

13. Lewis, T.; Drury, A. N.; Wedd, A. M., and Iliescu, C. C.: Observations upon the Action of Certain Drugs upon Fibrillation of the Auricles, Heart **9**:207, 1922.

14. Viko, L. E.; Marvin, H. M., and White, P. D.: A Clinical Report on the Use of Quinidin Sulphate, Arch. Int. Med. **31**:345 (March) 1923.

the circus movement in patients who had been previously digitalized. Wolff and White [15] observed that, theoretically, digitalis in suitable doses might favor the restoration of a normal rhythm by quinidine, and were of the opinion that such was the case in a group of their patients, although the very small number of their cases and the slight difference between the two groups seem insufficient to justify the conclusion. They did not observe any undesirable symptoms in patients with auricular fibrillation which they could attribute to the combined action of the two drugs. Levy [16] observed ventricular tachycardia five times after quinidine in a series of twenty-five patients with auricular fibrillation. The procedure prior to quinidine was to restore compensation by various factors in addition to digitalis if necessary. It is possible, therefore, that the ventricular tachycardia may not have been due to quinidine, but to the combined action of large doses of digitalis and quinidine, although Levy ascribed the result to quinidine alone. It is well known,[17] for example, that a potential rapid idioventricular rhythm as the result of digitalis may be held in abeyance by a rapid supraventricular pacemaker, and the suppression of such a pacemaker will bring into view a ventricular tachycardia. The latter might therefore be due to the action of digitalis on the ventricle, which would become evident only after quinidine had induced an A-V block or auricular standstill.

In a more recent study of the use of quinidine in chronic auricular fibrillation, Maynard [18] listed, among observations on the toxic effects of quinidine, ventricular premature contractions which occurred in short runs in some patients, an attack of ventricular paroxysmal tachycardia, one case of bigeminal rhythm, and two cases of transient bundle branch block. He found that impaired A-V conduction occurred quite regularly when the normal rhythm was established. All these effects may be produced by digitalis alone, and none of them has been produced by even larger doses of quinidine alone in the normal unanesthetized dog. This is not intended to suggest that quinidine was not directly responsible for the effects in these patients, but to justify the question as to what part the action of digitalis may have played. The paper makes no mention of the use of digitalis in the group of patients as a whole, with the exception of a casual reference to its use in a fatal case, although one would be justified in suspecting—unless the state-

15. Wolff, L., and White, P. D.: Auricular Fibrillation, Arch. Int. Med. **43**:653 (May) 1929.

16. Levy, R. L.: Clinical Studies on Quinidine, New York State J. Med. **22**:276, 1922.

17. Gold, Lieberson and Gelfand.[5] Rothberger and Winterberg.[6]

18. Maynard, E. P.: Five Years' Experience in the Treatment of Chronic Auricular Fibrillation with Quinidine Sulphate, Am. J. M. Sc. **175**:55, 1928.

ment is made to the contrary—that of a large group of patients with auricular fibrillation followed for from one to five years, some had received digitalis.

There are numerous papers in the literature which bear directly on the same point, but the foregoing few will suffice to illustrate that, in general, insufficient attention has been paid to the matter of previous digitalization in clinical studies of the action of quinidine. The views on the uses and dangers of quinidine during the action of digitalis in man, with the one exception of their combined effect on the fibrillating auricle, are based almost entirely on inferences derived from a rather meager and inadequate experimental literature dealing directly with their combined actions. In many cases they are inferences from effects when the two drugs are used separately. Thus, the fact that quinidine can abolish fibrillation and digitalis can produce it led Frey [19] to advise against their use together in auricular fibrillation, although subsequent investigations left little doubt that this mechanism can be effectively abolished during the full action of digitalis. The same facts led Pezzi and Clerc [20] to recommend the use of quinine during the administration of digitalis in patients with a sinus rhythm to prevent auricular fibrillation, which the latter drug might provoke. They recommended it further to prevent other toxic effects of digitalis, such as coupled rhythm and extrasystoles, which they thought might be forerunners of ventricular fibrillation. They stated that they were unable to produce toxic effects with Nativelle's digitalin in dogs which had received quinine, but did not give any details of these experiments.

Schott,[21] in discussing the dangers of quinidine in man, warned against the combination of quinidine and digitalis because both depress A-V conduction, and he used as evidence the fact that conduction was depressed in his experiments with guinea-pigs after massive oral doses, about 1,500 mg. of quinidine per kilogram.

Weichmann [22] suggested the use of strophanthin intravenously to overcome the cardiac paralysis in man that may result from acute poisoning by quinidine. He based this suggestion on the results of experiments on the perfused heart of the frog in which, after quinidine had caused standstill, beating was reestablished by the addition

19. Frey, W.: Chinidin zur Bekämpfung der absoluten Herzunregelmässigkeit, Deutsches Arch. f. klin. Med. **136**:70, 1921.

20. Pezzi, C., and Clerc, A.: Action cardiaque de la quinidine, Presse méd. **28**:334, 1920.

21. Schott, E.: Zur Frage der Chinidintherapie, Deutsches Arch. f. klin. Med. **134**:208, 1920.

22. Weichmann, E.: Untersuchungen über das Chinidin, seine Antagonisten und Synergisten, Klin. Wchnschr. **34**:1683, 1922.

of strophanthin to the perfusion fluid. Cattell,[23] on the other hand, found that in the perfused frog's heart digitalis did not appear to modify the toxic action of quinidine, although when the order of the poisoning was reversed an antagonism was observed; namely, quinidine helped to revive ventricular contractions after they had practically ceased during the action of digitalis, and previous perfusion with dilute solutions of quinidine caused a delay in the subsequent action of digitalis with respect to the reduction in the amplitude of the contraction.

To elucidate the mechanism by which quinidine produces toxic effects in man, Frey and Hagemann [24] performed experiments on rabbits, from which they concluded that the essential toxic effect is a depression of the heart and that the injection of strophanthin neither prevented nor abolished the effect. Their results, however, have no application to the practical problem because they employed massive doses of both drugs, namely, from 72 to 100 mg. of quinidine lactate intravenously, and injections of 1 mg. of strophanthin to average sized rabbits.

Haskell [25] obtained interesting results in experiments on dogs, from which he concluded that quinidine may exert a favorable action on the abnormal rhythms induced by digitalis. His animals were anesthetized with such substances as ether, morphine and chlorbutanol, and records were taken with the myocardiograph or carotid blood pressure manometer; while it is true that quinidine was followed by changes in the rate and rhythm of the heart, there was no way, in the absence of electrocardiographic tracings, of ascertaining the mechanism of the heart beat following the quinidine and whether or not the changes were beneficial. The same applies to the study of Jackson, Friedlander and Lawrence,[26] who found that cardiac irregularities induced by digitoxin in dogs disappeared after the injection of quinidine.

Weiss and Hatcher [12] failed to detect synergism or antagonism between quinidine and ouabain in terms of the fatal doses in acute experiments in cats. This observation was made in the course of another study, and was not investigated further.

The present investigation was planned to study primarily the changes in cardiac mechanism under the combined actions of digitalis and

23. Cattell, M.: Observations on the Action of Digitalis on the Frog Heart and Its Modification by Quinidine, J. Pharmacol. & Exper. Therap. **27**:287, 1926.

24. Frey, W., and Hagemann, E.: Klinische und experimentelle Daten über toxische Chinidinwirkung, Ztschr. f. d. ges. exper. Med. **25**:290, 1921.

25. Haskell, C. C.: The Influence of Quinidine on the Cardiac Irregularity Produced by Digitalis, J. Pharmacol. & Exper. Therap. **32**:223, 1928.

26. Jackson, D. E.; Friedlander, A., and Lawrence, J. V.: An Experimental Investigation of the Pharmacological Action of Quinidine, J. Lab. & Clin. Med. **7**:311, 1922.

quinidine rather than to ascertain any synergism or antagonism between the two drugs in terms of doses that are fatal for normal animals. It appeared to us that the absence of antagonism expressed in terms of fatal doses, as some have found, would not exclude, *a priori*, the possibility of a beneficial action of quinidine in digitalis poisoning that might even avert a fatality resulting indirectly. To illustrate, ventricular tachycardia induced by digitalis in the normal cat or dog is usually not fatal. However, such an extremely rapid ectopic rhythm in the damaged heart of a patient may lead to heart failure and death, the cause of death therefore being the abnormal rhythm rather than direct depression by the drug. Hence, in such a case the mere abolition of the ventricular tachycardia by quinidine, if that were possible, might give an indication of an important antagonism to the fatal action of digitalis that would not be in evidence in the normal animal.

The results of the present study show that during the action of digitalis in the normal dog, quinidine produces effects on the auricle and ventricle which may result in an apparently favorable antagonism to the toxic effects of digitalis. Thus, in a case in which the latter has induced a ventricular tachycardia, quinidine may abolish this ectopic rhythm and at the same time slow the sinus, reestablishing a normal sinus rhythm with a rate that is considerably slower than the ectopic rhythm that was abolished. Such an antagonism should prove useful in suitable cases in man. An examination of the details of our results, however, shows further that because of the marked variability in the effects of digitalis and quinidine in varying doses, the combination of actions of quinidine that can prove useful in antagonizing the toxic effects of digitalis is exceedingly difficult to obtain, and that more often the injection of quinidine is followed by effects that are undesirable. In so far, then, as these results have any bearing on the clinical problem, they show that the use of quinidine to abolish the ventricular tachycardia induced by digitalis, while it may occasionally prove effective, presents dangers.

These experiments have, however, brought up certain interesting questions relating to the behavior of the heart under the influence of digitalis and quinidine, and we believe that the results throw light on the mechanism involved in some of the effects of both drugs that on the surface appear somewhat perplexing.

We have shown that digitalis alone causes a ventricular tachycardia and when the latter is abolished the ventricle frequently seems temporarily incapable of automatic activity. This is similar to the behavior of the ventricle after the sudden production of complete heart block.[27]

27. Erlanger, J., and Hirschfelder, A. D.: Further Studies on the Physiology of Heart-Block in Mammals, Am. J. Physiol. **15**:153, 1906.

The marked acceleration of the ventricle which occurs during digitalis poisoning is commonly referred to as an increased rhythmicity. This might be interpreted merely as an increase in the speed of the normal automatic "centers" of the ventricle,[6] while some have regarded the tachycardia as arising from an abnormal mechanism in the ventricle, such as a circus movement.[28] It is possible that the mechanism of the rapid idioventricular rhythm is not the same with different degrees of digitalis poisoning. If it were merely a matter of normal "centers" (those that excite the ventricle in ordinary complete heart block) becoming more active as the result of the digitalis, one would expect that greater difficulty would be encountered in completely suppressing such rhythmic activity than in the case of the normal, slow automaticity of the ventricle. Yet in one of our experiments digitalis produced a ventricular tachycardia of 220 a minute, and a reflex arising from the mere insertion of a needle into the vein promptly slowed and abolished this rhythm and induced a complete standstill of the ventricle for seventy-five seconds. Such is not the behavior of the slow idioventricular rhythm of complete heart block under the usual conditions. The assumption that the ventricular tachycardia induced by digitalis always represents an increase in the rhythmic activity of the normal automatic "centers" of the ventricle leads to the paradoxical conclusion that the greater the rhythmicity of the "center" the more readily is its activity abolished. It seems, therefore, more likely that, in many cases at least, it is an abnormal mechanism in the ventricle (produced by digitalis) which drives the latter at this rapid rate. The fact that in our experiments the ectopic rhythm usually disappeared abruptly and the fact that it did so after slowing to a fairly uniform point with varying doses of quinidine are suggestive of the behavior of a circus movement. But whatever the mechanism, the fact remains that during poisoning by digitalis alone, under special conditions these two changes in the ventricle may become evident: (1) An abnormal and exceedingly rapid pacemaker appears, and (2) there is depression of the normal automatic "centers" of the ventricle.

In the presence of A-V block induced by digitalis, doses of quinidine as low as 5 mg. sufficed to abolish the ventricular tachycardia, resulting frequently in prolonged periods of ventricular standstill. This action of quinidine was also seen in the animal described, in which the reflex alone was effective, and the results after quinidine in this case were indistinguishable from those produced by the reflex. Following quinidine in the digitalized animal, again two changes in the ventricle

28. (*a*) Palmer, R. S., and White, P. D.: Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in Direction of Ventricular Complexes in the Electrocardiogram, Am. Heart J. **3**:454, 1928. (*b*) Luten, D.: Clinical Studies of Digitalis: III. Advanced Toxic Rhythms, Arch. Int. Med. **35**:87 (Jan.) 1925.

become manifest: (1) abolition of the abnormal mechanism causing the disappearance of the ventricular tachycardia, and (2) depression of the normal automatic "centers" of the ventricle.

With respect to the ventricular tachycardia, therefore, quinidine exerts actions antagonistic to those of digitalis, the one abolishing the ectopic rhythm induced by the other. The ventricular standstill, however, that results from the two combinations, digitalis-reflex and digitalis-quinidine, does not lend itself to such a direct explanation. There is no known direct action of toxic doses of digitalis on the mammalian heart that would lead one to infer a direct depressant effect on the automatic activity of the ventricle. As for quinidine alone, there are several studies [29] which show that in the dog this drug does not readily depress this function. When fatal doses of quinidine were given to dogs under ether anesthesia the last signs of cardiac activity consisted in a slow rhythmic beat of the ventricle.[29a] In our own experiments it was a rather striking fact that the standstill of the ventricle after small doses of quinidine lasted no longer than after a sudden reflex stimulus, and after large doses of quinidine it lasted no longer than after small doses of the drug. The reverse would be expected if the standstill resulted from a direct action of the drug on the ventricle. These facts make it impossible to ascribe the ventricular pause to a direct depressant action of digitalis or quinidine on the ventricular rhythmicity without introducing the idea of an unusual type of synergism between the two drugs.

We believe that the explanation of the ventricular standstill is not to be found solely in any direct action of either of the drugs alone or in combination, but rather in certain facts relating to the behavior of the ventricle after rapid excitation that were described many years ago by Erlanger and Hirschfelder [27] and by Cushny.[30] The similarity between the results of Cushny's experiments and ours are extraordinary in view of the totally different conditions under which they were obtained. A close comparison of the details of these experiments leaves little doubt that the two sets of results have the same significance.

Cushny [30] showed that in the perfused heart of the cat and rabbit in which an idioventricular rhythm was established by severing the bundle of His, periods of rapid excitation of the ventricle by electrical shocks so fatigued the automatic activity of the ventricle that, when the external

29. (*a*) Cohn, A. E., and Levy, R. L.: Experimental Studies of the Pharmacology of Quinidine, Proc. Soc. Exper. Biol. & Med. **18**:283, 1921. (*b*) Drury, A. N.; Horsfall, W. N., and Munly, W. C.: Observations Relating to the Action of Quinidine upon the Dog's Heart; the Refractory Period of, and Conduction in, Ventricular Muscle, Heart **9**:365, 1922.

30. Cushny, A. R.: Stimulation of the Isolated Ventricle, with Special Reference to the Development of Spontaneous Rhythm, Heart **3**:257, 1912.

stimuli ceased, periods of ventricular standstill for as long as twenty seconds followed, and that sometimes the resumption of the spontaneous beating was interrupted by additional periods of standstill, indicating that the previous rapid excitation had rendered the automatic function more liable to fatigue. This occurred only when the ventricle was isolated from the impulses coming from the auricle. He showed further that while the period of rapid excitation had depressed conductivity and rhythmicity, the excitability and contractility of those hearts were not depressed because minimal stimuli applied during the pause still elicited a contraction of the ventricle of a magnitude the same as, or even greater than, that before the period of rapid excitation, and when the bundle of His had not been severed, the ventricular pause under the conditions of these experiments failed to occur. Others[31] have also shown that the automaticity can vary independently of the remaining functions of the heart.

As we have already indicated, practically identical results have been obtained in our experiments with the normal unanesthetized dog. The foregoing, therefore, afford a basis for a rational explanation of the effects of quinidine on the ventricle during the tachycardia induced by digitalis without material dependence on assumptions that have not received significant experimental support. Thus, by direct action digitalis induces an abnormal mechanism in the ventricle which drives the latter at a rapid rate in much the same way that electrical stimulation would, and as a result of this rapid excitation, the normal rhythmic "centers" of the ventricle are fatigued. The abolition of the abnormal rapid pacemaker by quinidine sometimes results, after a brief standstill, in a slow automatic rhythm of the ventricle which exhibits considerable fatigability, as shown by the very irregular rhythm and intermittent pauses. At other times ventricular standstill of long duration occurs, the inhibition of ventricular automaticity being due to the previous period of rapid excitation rather than to any direct action of the drugs. That the excitability of the ventricle has not been materially depressed by either of the drugs or by the period of rapid excitation is in evidence from the fact that if supraventricular impulses can reach the ventricle, the latter is capable of responding promptly to such impulses with a rate as rapid as 220 a minute; hence, in the absence of complete heart block, a small dose of quinidine after abolishing the ventricular tachycardia does not produce ventricular standstill but a sinus rhythm.[32]

31. Herring, H. E.: Ueber die Unabhängigkeit der Reizbildung und der Reactionsfähigkeit des Herzens, Arch. f. d. ges. Physiol. **143**:370, 1911.

32. Complete cardiac standstill may result, even in the absence of A-V block, if the dose of quinidine has been large enough to cause auricular asystole as well.

When death results after the administration of quinidine under such conditions as in these experiments, it is therefore to be ascribed, not to a direct action of the two drugs, but rather to the inhibition of the automatic activity of the ventricle resulting from the rapid idioventricular rhythm induced by digitalis. This distinction is emphasized because it appears to be of more than academic interest. Quinidine has been employed from time to time for abolishing ventricular tachycardia in man arising under various pathologic conditions.[2] Ventricular tachycardia is occasionally produced by the toxic action of digitalis in man.[28b] We have shown that experimentally this toxic rhythm induced by digitalis may be abolished by quinidine. Our results also show, however, that this use of quinidine may cause death, and on the basis of one of the probable mechanisms by which this comes about, they indicate, further, that the treatment with quinidine of ventricular tachycardia, from whatever cause, in the presence of an A-V block may be dangerous, because in this condition the abolition of the abnormal rhythm may be followed by a state of the ventricle that is much more serious, namely, complete ventricular arrest.

We cannot venture an explanation, at this time, of the reaction of the auricle to quinidine during the action of digitalis. We have assumed that the rapid auricular rhythm resulting from digitalis poisoning is a simple tachycardia of sinus origin. It is a rather striking fact that total doses of quinidine alone up to 40 mg. cause only auricular acceleration, whereas doses as small as 3 mg. during digitalis poisoning may cause auricular standstill. The mechanism involved requires further investigation.

SUMMARY AND CONCLUSIONS

1. Sixteen experiments were carried out to study the effects of quinidine in varying doses given intravenously (intramuscularly in one experiment) on the ventricular ectopic rhythms induced by digitalis in eleven normal unanesthetized dogs.

2. Although quinidine, even in very large doses, produces no change in the cardiac rhythm other than sinus acceleration in the normal dog, in the one in which digitalis has produced a ventricular tachycardia quinidine may accelerate or slow the heart rate, change the rhythm from one that is regular to one that is very irregular, or vice versa, and induce tetanic convulsions.

3. The aforementioned effects are due to one or more of the following changes in the cardiac mechanism: slowing of the ventricular tachycardia, abolition of the ventricular tachycardia, auricular or ventricular or complete cardiac standstill, establishment of a nodal rhythm or slow idioventricular rhythm or reestablishment of a normal sinus rhythm.

4. Changes in the regularity or irregularity of the rhythm are no guide as to whether a desirable or an undesirable change in the cardiac mechanism has occurred, as revealed in the electrocardiogram.

5. Doses of quinidine that are harmless to the normal unanesthetized dog may produce death as the result of ventricular standstill in the dog in which digitalis has induced a ventricular tachycardia.

6. The auricle (or sinus) also becomes very sensitive to depression by quinidine during the action of digitalis, so that doses which produce only acceleration of the auricle in the normal dog may produce auricular standstill during the auricular tachycardia resulting from digitalis poisoning.

7. The foregoing effects may be produced by very small doses of quinidine, comparable to those used intravenously in man, namely, the equivalent of about from 2 to 6 grains (0.13 to 0.39 Gm.) for man.

8. These effects of quinidine usually come on within less than a minute after the intravenous injection and are of very short duration, lasting only a few minutes in most cases. In a few instances some of them have been prolonged for considerable periods, with occasional interruptions, by repeated injections.

9. The effects of quinidine vary not only with the dose of this drug but with the intensity of the digitalis poisoning. If digitalis has caused ventricular tachycardia without A-V block, quinidine will usually reestablish a normal rhythm (sinus [?] tachycardia). If digitalis causes an A-V block in addition, quinidine may now produce ventricular standstill after the ventricular tachycardia has been abolished.

10. If small doses of quinidine fail to induce a normal sinus rhythm, large doses also fail to do so because under these conditions A-V block is usually present (masked by the ventricular tachycardia), and the effect of the quinidine, after slowing of the ventricle, is ventricular standstill.

11. Ventricular standstill, sometimes for periods up to a minute or longer, as the result of relatively small doses of quinidine is common in the dog in which digitalis has produced a ventricular tachycardia.

12. While in the normal dog large doses of quinidine induce clonic convulsions, two types of convulsions occur after quinidine in the overdigitalized dog, those appearing after small doses being tonic in character and due to prolonged periods of ventricular standstill.

13. Double vagotomy does not appreciably alter any of these phenomena.

14. While quinidine may produce a temporary desirable antagonistic effect in the case of ventricular tachycardia resulting from digitalis

poisoning, the difficulty of obtaining the necessary combination of actions and the possibility of producing ventricular standstill render its use dangerous for this purpose.

15. The probable mechanism of the ventricular standstill after quinidine during digitalis poisoning is described.

16. It is indicated that the use of quinidine to abolish ventricular tachycardia from any cause is dangerous in the presence of A-V block.

Book Reviews

Entstehung, Erkennung und Behandlung innerer Krankheiten. By Ludolf Krehl. Volume 2. Second edition. Price, 12.80 marks. Pp. 192. Berlin: Julius Springer, 1932.

This is the second of a three volume work on the pathogenesis, diagnosis and treatment of the diseases of internal medicine. The first volume of the trilogy was recently reviewed in the ARCHIVES; the last volume is still to come. The author, Dr. Ludolf Krehl, for twenty-six years professor and head of the Medical Clinic of Heidelberg, is one of the great figures in German medicine. The present volume deals with diagnosis; it is excellent reading for the initiated, but cannot be recommended as a textbook; in fact, it cannot be intended for the beginner. Rather is it a charming essay, a fireside chatting, what a practitioner might expect to hear were he to enjoy an intimate visit with the master clinician, a confiding of the secrets of the trade and an exposition of those methods of procedure found effective.

The table of contents suggests a more systematic treatment of the subject than actually exists. The introductory sections deal with the art of diagnosis and clinical decision. The literature of the last twenty years is filled with contention as to whether medical procedure is science or art. Krehl is content to be a physician. Although the practice of medicine is largely built on scientific thought and method, the physician must go further than science is able to follow. Hesitation and doubt are necessary attributes of the scientist, but the physician must know his mind and act with resolution; intuition is required, an understanding of social difficulties and emotional conflicts; tact is indispensable, with an abundant sympathy. Krehl deplores the socialistic direction of modern medicine, especially in the German "Krankenkasse," whereby the relationship of patients to physicians becomes that of delinquents to a judge.

An intimate investigation of the psychic should be a part of every examination, a "psychoanalysis," not in the sense of the cult, but according to the true meaning of the word, and only when necessary. The vogue for indecent inquiry into the deeper processes of the soul is deplored as being frequently unnecessary and commonly harmful; it must do injury to sensitively organized persons. Everything here depends on the tact and insight of the physician who should do that which is required for elucidating the difficulties encountered, but nothing more.

The subsequent chapters are devoted to a critical discussion of the methods of examination and to the differential diagnosis of fever, the infectious diseases, the blood, the circulation, the respiration, the digestion, diseases of the kidneys and urinary tract, the nervous system, the muscles and the bone. Each topic is considered without an attempt at exhaustive or systematic treatment, but discursively and intimately as in informal conversation. The reader will feel amply repaid for the time he spends with these pages.

[EDITOR'S NOTE: A review of volume 1 of this triology was published in the September, 1932, issue of the ARCHIVES, p. 507. The title of this volume is "Pathologische Physiologie."]

Clinical Endocrinology of the Female. By Charles Mazer, M.D., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to Mount Sinai and Northern Liberties Hospitals, Philadelphia, and Leopold Goldstein, M.D., Demonstrator of Obstetrics, Jefferson Medical College; Assistant Gynecologist to Mount Sinai Hospital; Formerly Fellow in Gynecologic Research, University of Pennsylvania. Cloth. Price, $6 net. Pp. 518, with 117 illustrations. Philadelphia: W. B. Saunders Company, 1932.

One of the most striking developments of recent medicine is the revolution that has taken place in ideas on gonadal function in relation to hormonal control

While the idea has gradually developed that such processes as menstruation, pregnancy and parturition, as well as aberrations from the normal course of these processes, are influenced by hormonal activity, the subject has been for the most part shrouded in mystery and has been confused by obviously futile and irrational "endocrine" therapy. Only in recent years has some suggestion of reason begun to flow from orderly and purposeful animal experimentation in this domain. As a matter of fact, so violent now is the torrent of publications and so bitter are the disagreements among able workers that one hardly dares hope that order can as yet emerge out of chaos.

In this well written, soundly tempered monograph one is tempted to say that the writers have achieved the impossible. Much of the material will doubtless require eventual revision—the subject is in too much of a state of flux for definitive treatment—but the statements are conservative and, above all, are documented by a scholarly and well selected bibliography. There is in brief, a summary of the fundamental physiology of the endocrine glands in relation to gynecology, as the matter stands today, with well reasoned applications to the various clinical disorders of the female genital processes. The reviewer feels that the book is unique in its field and is a storehouse of invaluable information for the physician who faces these distressing and perplexing problems.

Herz- und Kreislaufinsuffizienz: Ein kurzes System der Störungen im Kreislaufsapparat. By Dr. K. F. Wenckebach. Band III. Price, 8 marks. Pp. 120. Dresden: Theodor Steinkopff, 1931.

This "Büchlein" is one of a series of monographs designed primarily for the "praktischen Arzt," although, as Wenckebach adds, it may be of value to "Studierende" and to the "Kreislaufforscher." It presents an excellent, critical summary of the modern physiologic, biochemical and clinical aspects of circulatory failure.

Under cardinal circulatory disturbances it discusses failure of the left side of the heart, obstructions in the pulmonary circuit and failure of the right side of the heart. It appraises the importance, in the reverse order of the circulation, of obstruction of the great veins, the small veins and capillaries and, finally, the arterial system.

The second portion of the monograph is given over to a discussion of certain secondary aids to the circulation—"Muskelarbeit," respiration, the peripheral heart, etc.—a discussion of water balance, body metabolism and blood volume and a final chapter on digitalis therapy and dyspnea.

The reviewer found himself particularly interested in the discussion of oxygen disturbance, anoxemia, coronary obstruction, cardiac infarction, etc., although possibly not being entirely in agreement with Wenckebach's views on spasm of the coronary artery. Similarly, he finds himself in agreement with the statement of the frequency of coronary thrombosis and the infrequency of coronary embolism as causes of cardiac infarction, but looks in vain for emphasis on the findings of single or multiple calcified sclerotic plaques alone (without thrombosis) as the cause of complete coronary occlusion with subsequent myocardial infarction.

Wenckebach has written, characteristically, a fine, lucid review of the salient topics of circulatory failure. One can wholeheartedly and enthusiastically recommend this monograph to those interested in this field of disturbed cardiac physiology.

Fractures. By Maurice Sinclair, C.M.G., M.B., B.Ch. (Edinburgh). Edited by G. Gordon Taylor, O.B.E., M.A., F.R.C.S. Price, 24 shillings. Pp. 539, with 337 illustrations. London: Constable & Co., Ltd., 1931.

This is a textbook on fractures for the practitioner. It is prefaced by a plea for improvement in the treatment of fractures generally, based on better knowledge of the fundamentals of anatomic relationships and practical mechanics. "Ninety per cent of good anatomical results are followed by good functional results" is the continuous emphasis made in this book.

The book is divided into two almost equal parts, the first dealing with general considerations, such as the principles of treatment, the influence of age and disease, signs and symptoms of fractures, repair of fractures, roentgen appearances, massage and movements, the end-results, complications, such as deformities and ununited fractures, the selection of the type of treatment, open operations, bone grafts, amputations, artificial limbs and medicolegal questions. Of these, the chapters on open operations and bone grafts are especially well written and contain information that would be difficult to locate elsewhere, with so little effort.

The second half discusses the treatment of individual fractures. Special emphasis is given to the management of fractures of long bones, clearly showing, with illustrations, the use of splints and appliances for obtaining the desired positions for the best end-results. In this field, the reviewer knows of no better text anywhere, because of the simple and clear way with which the subject is dealt. The chapters on the treatment of pelvic and skull fractures, in comparison with the rest of the book, are incomplete.

The book is richly illustrated with 337 x-ray photographs, photographs and diagrams. While knowledge of anatomy and the application of this knowledge are emphasized as requisite to successful treatment of fractures, no great amount of space is devoted to anatomic considerations. It is a practical textbook on treatment and, as such, is one of the best.

The Sputum: Its Examination and Clinical Significance. By Randall Clifford, M.D. Price, $4. Pp. 167, with 21 illustrations in black and white and 7 colored plates. New York: The Macmillan Company, 1932.

To the physician who is accustomed to order the sending of a specimen of sputum to the laboratory for examination as a routine procedure and does not get first hand knowledge of the appearances of these various types of disease exudates, the contents of this monograph will quickly prove to him that he has neglected a major portion of his part of the clinical examination. It has been repeatedly shown that the physical signs commonly depended on by the clinician to diagnosticate pulmonary disorders originate in the first few millimeters of depth from the surface and as practically all of the morbid processes dealt with are exudative, it is readily apparent that much pertinent information may be obtained from a close ocular examination of the sputum. The trend of the modern physician to relegate this examination to the laboratory is a step backward. Probably the most accurate knowledge of the degree of severity of an inflammatory process is expressed in the quantity of purulent material produced. Very few modern hospital charts show such information.

To those laboratory workers who are content merely to report sputum as "negative" or "positive" for tubercle bacilli, a close study of the subject matter presented will reveal many sins of omission that may have meant life or death for many a patient. How often does one see elastic tissue reported? Yet the prompt recognition of this sign of degeneration of pulmonary tissue is of the utmost importance.

The text is well written, the interpretations of the findings are well supported by references, and the colored plates are particularly well executed.

Fraktionierte Lumbalpunktion bei otogenen Meningitiden. By Aage Westergaard, Copenhagen. Pp. 213. Kopenhagen: Nyt Nordisk Forlag, Arnold Busck, 1931.

By fractional lumbar puncture is understood the removal of liquor cerebrospinalis in a number of separate portions. It is a diagnostic procedure which the author of this book has elaborated and discussed in the minutest detail from observations on seventy-three patients, covering a period of four years.

The method is simple enough. The patient is placed in the right lateral prone position on a table the head end of which is elevated 30 cm., the knees being drawn up in the usual manner.

The puncture is made with 1.2 mm. and 1.5 mm. (external diameter) needles, respectively, for children and adults. The interspaces utilized are not mentioned, but presumably are the third and fourth lumbar. The liquor is collected in six portions of from 2 to 3 cc. or 3 to 4 cc. and immediately stoppered. The cells are then stained in the diluted fluid with a solution containing methyl violet and glacial acetic acid in definite proportions, and the number determined with the Fuchs-Rosenthal counting chamber. The results of these counts are graphically expressed in terms of unit volumes of cerebrospinal fluid.

Claims made are that the method is of clinical value in determining the prognosis of a meningeal infection, a rising curve denoting a diffuse meningitis. On the other hand, a declining or horizontal curve indicates a circumscribed process or perhaps that a diffuse meningitis is subsiding and becoming circumscribed. In the event that definite symptoms persist after an operative procedure with a horizontal or declining cell curve in the liquor, an endocranial abscess should be suspected.

Man and Medicine: An Introduction to Medical Knowledge. By Dr. Henry E. Segerist, Professor at the University of Leipzig. With an Introduction by Dr. William H. Welch, Professor of the History of Medicine, The Johns Hopkins University. Translated by Margaret Galt Boise. Cloth. Price, $4. Pp. 340. New York: W. W. Norton & Company, Inc., 1932.

This book is an outline of the history and the development of medicine. When the medical reader turns the final page, he cannot be sure whether the author has been binding laurel to the plow or gilding the lily.

Beginning with Vesalius, the development of medicine is traced faithfully to its present state of advancement. The book is beautifully written, the literary style is excellent, and the scientific accuracy of detail bears witness to the author's knowledge of the subject, and perhaps gives a clue to his Teutonic antecedents. But there is a certain lack of imagination, a lack of inspirational or emotional push that one expects to find in works of this sort. This is doubtless due to the author's insistence on accuracy. Scientific accuracy and inspirational appeal are often incompatible. A recitation of more or less well known facts, even when expressed in such excellent style, is likely to leave the medical reader cold.

For the lay reader who wishes an authoritative and accurate outline of the development of medicine, written in terms that may be easily understood, this work cannot be too highly recommended.

Fungous Diseases: A Clinico-Mycological Text. By Harry C. Jacobson. Price, $5.50. Pp. 317. Springfield, Ill.: Charles C. Thomas, 1932.

The subject of mycotic infections is rather a terror to most physicians, perhaps because of the inaccessibility of usable information. The brief comments found in most textbooks are obviously inadequate, whereas the large compendia are unintelligible to the average physician, who usually becomes lost in a plexus of terminology and in the well known disputes about classification. Hence the reviewer approached the present work, designed especially for the clinician, with hope and enthusiasm; his hopes were to some extent realized so far as the subject is reduced to a simple and yet reasonably comprehensive level. The author has a sound idea, but unfortunately the writing is marred not only by frequent errors in grammar, but by an obscure, redundant and at times unreadable style. The format of the book is attractive; the illustrations are abundant and well selected, and the bibliography is adequate. The sections on therapy could be improved by a more critical evaluation of various measures and by more detailed instructions as to drug dosage and procedure.

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